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GRAPHIC AND LABORATORY DIAGNOSIS IN CORONARY DISEASE

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Many laboratory aids are now available to help in the diagnosis of coronary artery disease. The electrocardiogram can show the difference between coronary insufficiency, sometimes considered as a small coronary occlusion, and the large coronary occlusion. The former is often preventable and has a favorable prognosis. Coronary occlusion has no specific treatment. Other tests such as determination of muscle enzymes in the blood, the vectorcardiogram, and roentgenography are also available to assist in determining the specific clinical diagnosis.

IN PREVIOUS YEARS, the diagnosis of coronary artery disease depended almost entirely on the clinical acumen of the doctor. He carefully and skillfully took a history and made a thorough examination. Today, however, in addition to a thorough anamnesis, many laboratory aids are employed which have proved of invaluable aid in diagnosis. These include electrocardiography, roentgenography, fluoroscopy, electrokymography, vectorcardiography, and muscle enzyme studies. In fact, there are times when one or more of these means may prove to be all decisive.

The electrocardiogram has proved itself capable of identifying abnormalities that are pathognomonic of acute coronary artery occlusion. It may distinguish between an acute abdominal emergency necessitating surgical intervention and an acute coronary occlusion requiring immediate rest. It may disclose evidence of an unsuspected previous coronary occlusion, the so-called silent occlusion. Acute indigestion, which frequently simulates coronary occlusion, is excluded by the electrocardiogram.

The electrocardiogram has clarified the differential diagnosis between a "small" coronary occlusion versus a "large" one. We now know the former indicates a mild heart attack and perhaps not an occlusion at all; it is usually coronary insufficiency. This latter entity is a very common form of heart attack and, fortunately, in general, carries with it a favorable prognosis. It can often be prevented and even cured by proper therapy. Coronary occlusion, on the other hand, in the present state of our knowledge, is not preventable, nor is there any specific treatment for it. Thus, the electrocardiogram has made clear the distinction between angina pectoris, coronary insufficiency, and coronary occlusion, where hitherto there had been much confusion. This clarification will enable one to make a more logical study of the natural cause of coronary artery diseases which, in turn, will make for further progress in prevention and cure of heart diseases.

A patient may have a normal electrocardiogram on resting, and yet have coronary artery disease. Such an electrocardiogram merely indicates that the patient's circulation is adequate during this state of inactivity. It does not give any information as to the reaction of the heart when the person engages in ordinary activities such as walking and climbing or when he is subjected to emotional stress. The heart's reaction to the physical and mental strain of life is elucidated by the two-step exercise test. Again and again, a positive result from a single or double two-step exercise test has been found in

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people who present symptoms of an anginal syndrome but whose electrocardiogram on resting is normal. We all hear of a sudden unexpected heart attack or death in a man who was given a clean bill of health simply because his electrocardiogram on resting had been normal. This is to be deplored.

In regard to the determination of muscle enzymes in the blood as an indication of acute infarction of heart muscle, it does seem that it will help in doubtful and obscure cases. Since tests like the serum glutamic oxalacetic transaminase (SGO-T) test are quantitative; they yield not only the basic information as to whether or not infarction has occurred but also the extent of myocardial necrosis. The muscle enzyme studies will probably supersede the sedimentation rate determination.

The vectorcardiogram, which analyzes cardiac electromotive force on the unitarian dipole theory, has served to simplify both understanding and teaching of electrocardiography. In addition, it has clarified interpretation of right ventricular preponderance and block patterns. More precise localization of infarcts has also been claimed with the use of this technique.

Roentgenoscopy and roentgenokymography demonstrate the effect of muscle injury due to coronary occlusion on the function of the heart. The abnormality in cardiac contraction can be observed during fluoroscopy, or a permanent record can be obtained by the roentgenokymograph. The "reversal of pulsation," when present during either procedure, is practically diagnostic of myocardial infarction.

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MASTER TWO-STEP TEST IN CORONARY ARTERY DISEASE

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The Master two-step test is a standardized exercise that permits the making of an electrocardiogram immediately after the activity terminates. The main criterion of the result is the behavior of the S-T segment of the tracing; depression of more than 0.5 mm. in any lead is considered a positive result. The test was applied to 186 patients known to have either angina pectoris or a healed myocardial infarction. By the criterion of ischemic S-T segment depression alone the test was positive in 61.3%; when Master's other criteria were also imposed, the test was positive in 81.7%. The test was applied further to 108 normal persons. By the criterion of ischemic S-T segment depression alone the test was negative in all; when Master's other criteria were also imposed, the test was positive in 19.4%. While a negative result does not exclude coronary insufficiency, a positive one strengthens the diagnosis of suspected coronary disease. Although the only conclusive evidence of coronary insufficiency is believed to be ischemic S-T segment depression, fewer cases escaped detection when all of Master's criteria were utilized. When sound clinical judgment is employed in conjunction with the test, overdiagnosis is infrequent.

In most instances the diagnosis of angina pectoris is made with ease and assurance from the history alone, without resort to electrocardiography. When, however, the quality, site, distribution, duration, or relation to effort of a chest pain that is suggestive of angina pectoris does not conform to classic concepts, a reliable objective test is needed. The finding of abnormalities in the electrocardiogram recorded at rest may add to the examiner's suspicion that a patient suffers from angina pectoris insofar as these may indicate prior myocardial damage. Confirmation by this means, however, is frequently lacking, since the 12-lead resting electrocardiogram is normal or borderline in well over one-third of known cases of angina pectoris. Furthermore, since some 78 different conditions other than coronary insufficiency might on occasion simulate the anginal syndrome,[1] whereas the latter frequently does not conform to Heberden's classic description,[2] diagnostic error is often unavoidable with usual methods of examination.

It is true that a normal resting electrocardiogram may attest to the adequacy of the coronary circulation under the work load of the resting state, but such normality does not also signify that coronary reserve is capable of meeting the metabolic demands of the heart under the stress of daily life. Ideally, therefore, electrocardiographic records should be obtained during a spontaneous attack

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or after a reproduction of the circumstances which regularly provoke distress. Since this is not often practicable, stress tests have been devised to disclose evidence of relative myocardial ischemia by provoking the characteristic attack or engendering changes in the electrocardiogram. To have validity, such tests must distinguish electrocardiographic abnormalities from normal variations which appear after exercise or other stress in the absence of significant disease.

Normal Electrocardiographic Variations

A number of influences, exclusive of anoxemia and ischemia, lead to depression of the S-T segment and flattening and even inversion of the T wave. Thus, increased activity of the sympathetic nervous system can produce such changes, and patients with neurocirculatory asthenia and anxiety are prone to exhibit them. The S-T depression caused by tachycardia is well known. To a large extent, this is due to the increased size of the auricular T wave, but it may also be caused by differences in the rate of repolarization in the inner and outer layers of the myocardium. Consequently, tachycardia itself may involve deviations of the S-T segment which approximate in degree those which result from deep myocardial ischemia. Moreover, the possibility also exists that such changes are at times evoked by coronary insufficiency which is physiological and transient during adjustment to stress.[3] Hyperventilation by decreasing the carbon dioxide content of the blood has also been shown to lead to S-T depression and T-wave inversion.

It is essential to recognize, therefore, that these factors as well as the development of relative coronary insufficiency must play a role in the electrocardiographic criteria used in judging whether an exercise test is positive or negative. To have validity, the judgment of the test should be based on a comparison of the electrocardiographic changes in known cases of coronary insufficiency with those in known normal subjects. A satisfactory test should be strenuous enough to disclose even minor disturbances of the coronary circulation yet easy enough not to cause undue muscular fatigue in persons not accustomed to exercise. At the same time, it should be standardized to correct for the normal decrease of the coronary reserve with age. Of the many types and modes of application of exercise advocated as tests of coronary competence, only the two-step test of Master can at present qualify as a practical, reliable, and safe procedure.

The Master two-step test employs a simple technique.[4] It consists of stair-climbing, the most natural form of exercise, but in contrast to ordinary stair-climbing, it permits constant observation of the patient and allows the electrocardiogram to be inscribed immediately after termination of activity. Since it entails a routine type of work, fear and apprehension, which may invalidate tests of cardiovascular function, are held to a minimum. By extensive observation, Master has standardized the amount and rate of exercise according to age, weight, and sex and has established criteria for a positive test. In sharp contrast, other procedures frequently subject the patient to unnatural and excessive physical strain which may evoke psychic, mental, and physical reactions interfering with accurate estimation of cardiac function. Since such tests have not been standardized, they are often hazardous. There is no doubt that tests requiring the maximal effort of which the subject is capable afford the highest degree of specificity, but such procedures should not be countenanced because of the dangers attending their use.

Criteria of a Positive Master Test

It is fortunately not the purpose of the Master two-step test to induce angina, since it is indeed unwise to induce attacks of chest pain for diagnostic purposes. Consequently, in the interest of safety, peak diagnostic accuracy must be sacrificed. Nevertheless, Master[5] has reported that the single or double two-step test was positive in 96.8% of 250 consecutive patients with definite coronary disease. In contrast, he has found that the test has indicated abnormal responses in only 6 to 8% of normal persons. Master's main criterion for a positive test is an S-T depression of more than 0.5 mm. in any lead. He considers definite T-wave inversion as "probably abnormal" but regards minor T wave changes and transient arrythmias of no or little diagnostic significance.

Master's criteria have been widely used in the interpretation of the two-step test performed for the evaluation of patients suspected of having coronary disease and as a screening procedure to detect coronary disease in apparently normal persons. Although S-T depression and/or T-wave alteration have been included in most criteria for a positive test, there has been no agreement as to the amount of S-T depression that indicates abnormality. In studies of normal groups, a positive response by Master's criteria has been reported in as high as 25% of the cases studied.[6] Many recent investigators, therefore, have increased the criterion of a positive test to an S-T depression of 1 mm. or more in an effort to reduce the frequency of false-positive responses. Similarly, until recently, little importance had been attached to the configuration of the S-T segment (see figure), despite evidence that flat or sagging depression after effort denotes myocardial ischemia, whereas transitory depression of the S-T junction occurs normally after effort and is due usually to physiological changes associated with tachycardia or, in some cases, to the effect of a large negative auricular T wave. Obviously, evaluation of the significance of the various criteria suggested as indicative of a positive response must await the follow-up of large series of unselected consecutive cases for sufficient periods to ascertain the subsequent occurrence of coronary disease.

On the basis of such studies, Robb and associates and Mattingly and associates [7] have contributed significantly toward this end. From a careful follow-up of more than 1,000 consecutive patients over a period of seven years, they have confirmed the contention of Master that S-T segment depression in excess of 0.5 mm. represents an abnormal response. Thus, they observed that an S-T depression of 0.5 mm. to 1 mm. was associated with as high an incidence of coronary disease, as indicated by the development of fatal and nonfatal coronary thrombosis, as was a depression of 1 and 2 mm. Moreover, since these investigators discovered no significant correlation between T-wave changes alone, conduction disturbances, or arrythmias and the subsequent development of coronary artery disease, they concluded that S-T segment depression should be used in the future as the only criterion for an abnormal response.

Robb and associates [7a] have compared the ischemic type of S-T depression with the junctional type of S-T segment depression with respect to the subsequent incidence of coronary occlusion. They found the coronary death rate in the ischemic type of S-T depression group to be more than double that in the junction depression group. Consequently, they have concluded that transitory S-T junction depression after exercise associated with tachycardia is usually a normal finding, although in some cases in which such depression persists after exercise and the return of the heart rate to normal, it may be due to myocardial ischemia. The best and the only unequivocal criterion for a positive test indicative of coronary insufficiency in the postexercise electrocardiogram is, according to these authors, ischemic S-T segment depression in excess of 0.5 mm. in any lead.

Response to Exercise Test in Patients with Definite Coronary Disease

Investigator	Total Cases, No.	Diagnosis	Patients with Negative Results		Patients with Positive Results							
					Total (Master's Criteria)		S-T Depression				T Wave Changes	
							Segment		Junction			
			No.	%	No.	%	No.	%	No.	%	No.	%
Russek	186	Angina pectoris; myocardial infarction	34	18.3	152	81.7	114	61.3	26	14.0	12	6.5
Robb and associates	69	Angina pectoris	21	30.4	48	69.6	35	50.7	6	8.7	6	8.7

False-Positive Responses

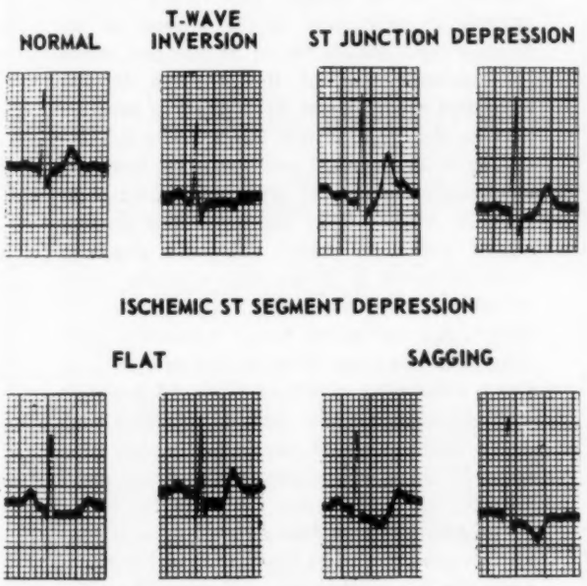
Thus, it is claimed that Master's criteria for an abnormal response, especially isolated T-wave change and transitory junctional S-T depression, are too inclusive and, due to the large percentage of false-positive results, frequently result in the overdiagnosis of coronary disease. The possibility of correcting such error by the use of stricter criteria is suggested by the findings in 108 normal persons under the age of 40 whom we studied by means of the double standard two-step exercise test. With Master's criteria 21, or 19.4%, of the entire group would be classified as abnormal reactors, whereas none would be so classified if ischemic S-T segment depression were the sole criterion of a positive test.

Nevertheless, the findings of Robb and Mattingly and their associates do not seem to justify the exclusion of S-T junction depression or isolated T-wave inversion as indexes of an abnormal response. In both categories, the coronary occlusion rates and the mortality from coronary disease were considerably higher than would be expected if these phenomena merely reflected a normal reaction to effort. Moreover, we have repeatedly observed S-T junction depression and ischemic S-T segment depression in the same patient under varying circumstances. In these cases the type of response has been closely correlated with the amount of stress or the coronary status at the time of testing. Many patients have been observed by us in whom a double two-step test evoked the ischemic type of S-T depression while lesser degrees of exertion produced only S-T junction depression. Both types of response, furthermore, could be prevented by the use of glyceryl trinitrate (nitroglycerine) prior to exercise. Similarly, in the natural course of the disease, it was not uncommon to find that one type of response with a specific amount of exercise had been replaced by the other. It should be recognized, therefore, that S-T junction depression is frequently an abnormal finding and that it commonly represents underlying myocardial ischemia of less intense degree than that which accompanies ischemic S-T segment depression. Since the latter usually denotes greater impairment of coronary circulation, a higher incidence of coronary occlusion and mortality rate was to be expected with this electrocardiographic abnormality.

Similarly, it appears unreasonable to disregard T-wave inversion as a criterion of positive response. It is well known that mild exertion lowers the T wave in normal subjects, but frank inversion of the T wave is infrequently seen in the absence of neurocirculatory asthenia, anxiety states, and other disorders associated with reflex augmentation of adrenergic influences. In a study of 108 normal individuals, Grossman and associates [8] did not observe a single instance in which an upright T wave became indiscernible or inverted. On the other hand, we have had occasion to record isolated T-wave inversion in several patients during spontaneous

attacks of angina pectoris and have been able to reproduce these changes by means of the Master two-step test. Consequently, in order to study the possible significance of T-wave inversion, minor T-wave changes which are normal, and sympathogenic distortions of the T wave which are functional, should be excluded from analysis.

Since the material studied by Robb and Mattingly and associates was derived chiefly from the Walter Reed Army hospital, neurocirculatory asthenia and anxiety states may have been present in unusually high incidence. This is assumed from the fact that most of their subjects were in the active military service and that their study was commenced during time of war. The inclusion of many such cases in a study designed to evaluate prognosis could give



Types of electrocardiographic response to double two-step exercise test (reproduced from Robb, Marks, and Mattingly [7a]).

rise to misleading results in a consideration of the significance of T-wave inversion or S-T junction depression, since both variations are commonly observed in these disorders.

By using Robb and associates' criterion of a positive test, namely, ischemic S-T segment depression, it is possible to avoid overdiagnosis of coronary disease, but many bona fide instances of this disorder will go unrecognized. With Master's criteria, false-positive results and overdiagnosis present a problem, but the test is capable of alerting the physician to the vast majority of cases of latent coronary insufficiency. Given this choice, I feel that it is far better for the clinician to overdiagnose the disease than to overlook it. With Master's criteria, a positive response to the single or double two-step test was recorded in 81.7% of 186 known cases of angina pectoris or healed myocardial infarction (see table). With the criterion of S-T segment depression alone, the incidence of positive response is reduced to 61.3%. Similarly, in the series of Robb and associates, the frequency of an abnormal response in 69 typical cases of angina pectoris was almost 70% with Master's criteria and only 50% by the newer definition.

The two-step exercise test, when properly executed and interpreted according to the criteria of Master, is a useful adjuvant in the differential diagnosis of coronary insufficiency. While a negative test does not exclude coronary insufficiency, a positive one strengthens this diagnosis. The only conclusive evidence of a positive test is ischemic S-T segment depression in excess of 0.5 mm. in any lead. Difficulty will be infrequently encountered if the physician remains aware of the normal and functional variations which occur in the electrocardiogram after exercise and if he views the test as but one of a series of evaluations which should lead him to his final judgment.

176 Hart Blvd.

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LABORATORY AIDS IN DIAGNOSIS OF MYOCARDIAL INFARCTION

CHANGES IN MUSCLE ENZYMES, ERYTHROCYTE SEDIMENTATION RATE, AND C-REACTIVE PROTEIN IN MYOCARDIAL INFARCTION

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The significance of certain enzymes in the serum (glutamic oxalacetic transaminase, glutamic pyruvic transaminase, and lactic dehydrogenase) was demonstrated by the experimental production of myocardial infarction and ischemia in dogs. The SGO-T (concentration of glutamic oxalacetic transaminase in the serum) was found to rise roughly in proportion to the amount of infarcted myocardium found at autopsy, while the concentration of the enzyme in the infarcted myocardium decreased in proportion to the age of the infarct. The SGO-T values in 297 of 300 patients after unequivocal acute transmural myocardial infarction rose to from 1.5 to 20 times the normal figure within 48 hours. All three enzymes were followed in 50 patients with the same condition and were found to increase in the serum, the elevation being especially prolonged in the case of lactic dehydrogenase. Data were also obtained from 50 patients with status anginosus, from 11 patients with acute pericarditis of varying etiology, and from 15 dogs with experimental impairment of coronary circulation. The behavior of these enzymes was found to differ in timing and in other respects from nonspecific reactions like the erythrocyte sedimentation rate, C-reactive protein, and plasma fibrinogen. Information from one group of tests therefore supplements that obtained from the other. If carefully interpreted they are of great diagnostic value.

The enzyme, glutamic oxalacetic transaminase, acts specifically to transfer the alpha-amino nitrogen of aspartic acid to alpha-ketoglutaric acid, thus bringing about the synthesis of a new amino acid, glutamic acid, and a new alpha-keto acid, oxalacetic acid. Acute transmural myocardial infarction is followed by an increase in the activity of this enzyme in the serum.[1] Since the activity of glutamic oxalacetic transaminase (GO-T) is 5,000 to 10,000 times greater in heart muscle than in serum and the activity of lactic dehydrogenase (LD) is 3,000 and of glutamic pyruvic transaminase (GP-T) 1,000 times greater, release of these enzymes from the damaged myocardium with its rich enzyme content probably accounts for the increase in serum activity following acute myocardial cell damage (table 1). These enzymes have been found to be present in all human serums tested and can be measured chromatographically, spectrophotometrically, and colorimetrically. Spectrophotometrically, a unit of activity is defined as a decrease in optical density of 0.001 mμ per milliliter per minute at 23 C.[2] The mean activity in human serums for SGO-T is 22.1 units ± 6.8, for SGP-T 16.0 units ± 9.0, and for SLD 400 units ± 200.

TABLE 1.—*Glutamic Oxalacetic Transaminase, Glutamic Pyruvic Transaminase, and Lactic Dehydrogenase Activity in Adult Human Tissues*

Tissue	GO-T,* Units per Gm.	GP-T, Units per Gm.	LD, Units per Gm.
Heart	156,000	7,100	222,000
Liver	142,000	44,000	95,000
Kidney	91,000	19,000	282,000
Serum	8-40	5-35	200-600

* Wet tissue.

SGO-T is stable in serum for four days at refrigerator temperatures and loses little activity if stored at these temperatures for as long as 30 days. The levels in the plasma and serum are the same and vary within experimental error from day to day in the same normal individuals. The reaction is unaffected by freezing or lyophilization, but heating to 100 C will destroy the activity. The SGO-T activity does not increase as a result of infectious, degenerative, neoplastic, allergic, reactive, or congenital disease states, or pregnancy or delivery, unless these are associated with acute damage to heart, skeletal muscle, liver, or possibly kidney. There is no consistent relationship between the SGO-T activity and the erythrocyte sedimentation rate, the white blood cell count, or the C-reactive protein or fibrinogen content of the serum. The type of hemolysis occurring during routine separation of serum from red blood cells does not significantly alter the SGO-T and SGP-T activity but may cause significant increase in SLD activity.

Myocardial injury results in a decrease of activity of SGO-T in the injured heart muscle and is reflected by a proportionate increase in the activity of

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the serum (fig. 1). The SGO-T activity rises following acute damage to skeletal muscle, liver, and kidney. Central nervous system injury has not been found to be associated with consistent increases in SGO-T activity. The SGO-T level rises precipitously after the patient's death and is highest in venous reservoirs draining tissues of maximal GO-T activity. Since SGO-T activity has been studied in many more patients with heart disease than has SGP-T or SLD, only brief mention of changes in the activity of the latter two enzymes will be made where data are available for comparison.

Myocardial Infarction

Experimental Studies.—The injection of plastic spheres through a balloon catheter in the aorta placed so that plastic spheres can be injected into the coronary sinus and hence into the coronary arteries produces a diffuse type of myocardial infarction. The SGO-T activity in all such experiments increased within four hours and reached maximal levels 5 to 30 times the control values within 9 to 23 hours after infarction. There was a relatively straight line relationship between the maximal or peak SGO-T level and the estimated amount of infarcted myocardium found at autopsy. For example, the dogs with maximal infarction had the highest SGO-T levels.[3] In rabbits, acute myocardial necrosis was produced by the intravenous injection of papain. The peak SGO-T activity was again roughly proportionate to the amount of myocardial cell damage found at autopsy.

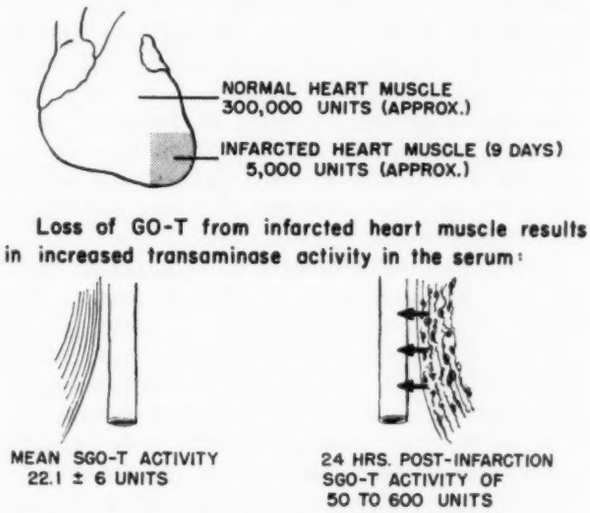
NORMAL HEART MUSCLE
300,000 UNITS (APPROX.)
INFARCTED HEART MUSCLE (9 DAYS)
5,000 UNITS (APPROX.)
Loss of GO-T from infarcted heart muscle results in increased transaminase activity in the serum:
MEAN SGO-T ACTIVITY
22.1 ± 6 UNITS
24 HRS. POST-INFARCTION
SGO-T ACTIVITY OF
50 TO 600 UNITS

Fig. 1.—Probable mechanism of increased SGO-T activity following acute myocardial infarction.

The skeletal muscle injury associated with thoracotomy causes increased SGO-T activity for four to seven days after surgery. Therefore, we produced myocardial infarcts in dogs by tightening a ligature 10 days after it had been placed about a coronary artery avoiding the surgical increase in enzyme activity due to trauma. The SGO-T activity rose within four to six hours in all animals sustaining infarcts produced by this method.

It was again noted that the higher the SGO-T activity, the larger the infarct; for example, the SGO-T peak from a 0.5-Gm. infarct was 64 units (24 above normal) and for an 18-Gm. infarct, 500 units.[4] The duration of abnormally increased but falling SGO-T activity was four to five days in animals with large infarcts and 24 hours when smaller areas of infarction were produced. In other words, both the height and duration of increased enzyme activity appeared to be proportional to the size of the infarct. Analysis of homogenes of the infarcted heart muscle showed a progressive decrease in GO-T activity with time which was proportional to the age of the infarct. Uninfarcted muscle from the same animal showed normal concentration of GO-T (table 2). In similar experiments on seven dogs sustaining 5 to 60-Gm. infarcts, the SGO-T activity increased 3 to 10 times, the SGP-T 3 to 5 times and the SLD 2 to 3 times normal.

TABLE 2.—*Transaminase Concentrations in Normal and Infarcted Heart Muscle in Experiments on Dogs*

Dog, No.	Concentration in Normal Muscle, Units/Gm.	Concentration in Infarcted Muscle, Units/Gm.	Age of Infarct	Ratio of Concentration, Normal: Infarcted Myocardium
1	200,000	...	...	...
2	305,400	220,400	2 hr.	1.3:1
3	451,000	218,600	20 hr.	2:1
4	465,000	23,000	7 days	20:1
5	348,000	33,200	7 days	11:1
6	250,000	5,600	9 days	45:1

Clinical Studies.—The SGO-T activity has been followed for 2 to 10 days in 300 patients after unequivocal acute transmural myocardial infarction. The SGO-T activity rose 1.5 to 20 times normal within the first 12 to 48 hours after infarction in 297 of these patients (fig. 2). In another group of patients whose serums were tested three or more days after the onset of infarction, the SGO-T activity was within normal limits in 60%, emphasizing the importance of blood sampling in the 12 to 48 hour postinfarc-

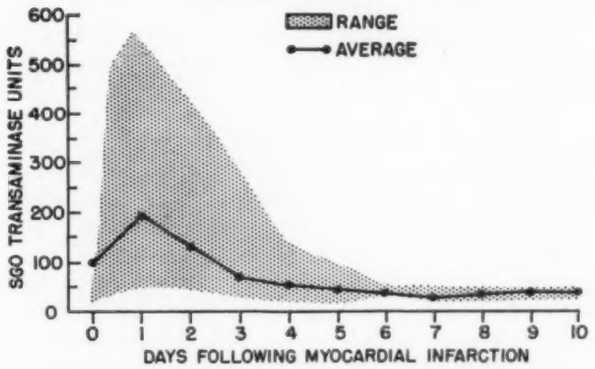

Fig. 2.—Range and average SGO-T activity following the onset of acute transmural myocardial infarction in 300 patients.

tion critical period when SGO-T activity is maximal. Secondary elevations of SGO-T were seen after recurrent chest pain due to extension of, or the development of, a new infarction in the same patient.[5]

In 50 patients with acute transmural myocardial infarction who had studies of the activity of all three enzymes, the SGO-T level rose 2 to 20 times normal, the SLD 2 to 10 times normal, and the SGP-T 1 to 3 times normal. The SLD activity remained elevated two to three days longer than the SGP-T activity [6] (fig. 3).

Left bundle branch block, previous healed myocardial infarction, and acute damage to so-called "silent" electrocardiographic areas of the heart make it difficult, if not impossible, to decide whether the chest pain of such patients is due to acute myocardial damage. It has been our experience that, when the transaminase is elevated, the clinical course of these patients has been such as to indicate that infarction had occurred. It is important in this group

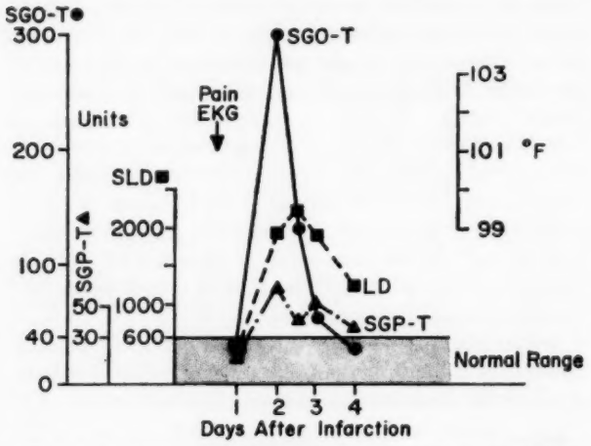

Fig. 3.—Average changes in SGO-T, SLD, and SGP-T activity following acute transmural myocardial infarction in a patient.

to test SGO-T activity as long as these patients experience pain, since infarction may often be delayed for several days. Several patients with chest pain and electrocardiographic evidence of subendocardial infarction have had increased transaminase levels and thus were treated as having had acute infarction, while in others, the enzyme levels were normal. In two the electrocardiographic abnormalities disappeared after digitalis was withdrawn.

There was a rough correlation between the SGO-T peak activity and the electrocardiographically estimated size of infarction in that patients with the highest enzyme levels had more extensive electrocardiographic changes. Peak activity above 350 units was frequently associated with a significant increase in mortality rate. No correlation has been found between the SGO-T activity and the white blood cell count, erythrocyte sedimentation rate, the location of the infarct, or the use of anticoagulant drugs, digitalis, antibiotics, sedatives, or pressor agents. Some observers have reported that acute congestive heart failure associated with marked liver engorgement may be associated with significant SGO-T elevations. Minor SGO-T elevation has been noted after prolonged bouts of paroxysmal tachycardia.[5] SGP-T activity increases proportionately less than SGO-T following injury to heart muscle but is more elevated following acute liver cell injury. SLD activity, however, is relatively unaffected by liver cell injury but rises following heart muscle or skeletal muscle damage in parallel fashion to SGO-T.

Angina Pectoris and Coronary Insufficiency

Myocardial ischemia was produced in 15 dogs by lifting a ligature placed 10 days previously under a coronary artery so as to cause marked T-wave and ST-segment changes but no Q-wave changes. Four of these animals developed subendocardial infarction, and all had elevated SGO-T activity. In 10 animals the SGO-T activity did not rise, and no microscopic evidence of heart muscle cell injury was found despite the appearance of temporary electrocardiographic evidence of ischemia manifested by ST-segment and T-wave changes. In one dog the SGO-T activity rose slightly, although no gross or microscopic evidence of myocardial infarction could be found.

Angina pectoris of variable duration has not been followed by an increase in SGO-T activity. The SGO-T activity was studied in 50 patients with coronary insufficiency or status anginosus whose electrocardiograms showed evidence of ischemia as manifested by moderate to marked T-wave inversion sometimes associated with ST-segment changes but without Q-wave abnormalities. The SGO-T activity remained within normal limits in 34 of these patients despite the persistence of prolonged substernal pain. The SGO-T activity rose in 16 of these patients suggesting that acute heart muscle cell damage had occurred. In eight instances pain had been present for three to six days before the SGO-T activity increased, indicating that severe anginal pain may be present for several days before myocardial necrosis or actual arterial occlusion occurs [5] (fig. 4 and 5).

Acute Pericarditis, Rheumatic Carditis, and Pulmonary Infarction

The SGO-T activity was followed daily or oftener in 11 patients with unequivocal evidence of acute pericarditis of varying etiology, and it remained within normal limits in 9 patients throughout the period of study. Two exhibited minor increases in SGO-T activity which was thought to be due to the presence of coexistent liver disease due in one instance to infectious mononucleosis and in the other to leukemia.[7]

The SGO-T activity in acute rheumatic fever without carditis does not increase. In some, but not all, patients with extensive rheumatic carditis, the SGO-T activity was increased. It is to be noted that the administration of large doses of aspirin to children will also cause elevation of the SGO-T activity.[8]

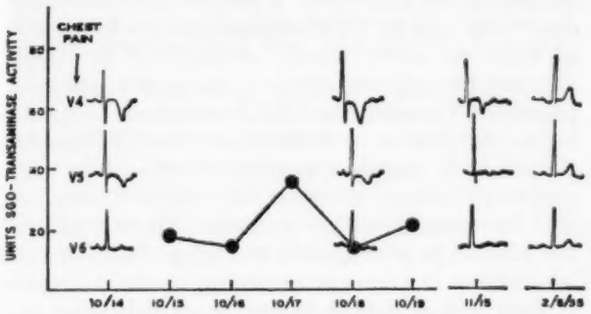

Fig. 4.—Marked, reversible electrocardiographic abnormalities in a patient with incapacitating angina recurring every 30 minutes from Oct. 8 to Oct. 20. The SGO-T level remained normal.

The SGO-T activity was followed during the course of pulmonary infarction in seven patients and remained at normal levels in all but one patient whose peak enzyme activity was 80 units.[7]

Comment

The spectrophotometric method employing the Beckman DU spectrophotometer is the most rapid and accurate method for the analysis of SGO-T, SGP-T, and SLD activity, but the Bausch and Lomb spectrophotometer with the use of Steinberg's modified technique (for SGO-T) is more economical and practical for smaller laboratories. Colorimetric methods for all three enzymes have been devised and can be done using equipment already available in most hospital laboratories. The serum should be separated promptly from the red blood cells, avoiding hemolysis, and then stored at refrigerator temperature for not more than four days. It is important to emphasize that unless blood is drawn within three days after the onset of infarction, the SGO-T activity cannot be relied upon as evidence of acute myocardial damage.

It is worth reemphasizing that SGO-T activity is not increased as a result of infectious, degenerative, neoplastic, allergic, reactive, or congenital diseases or pregnancy unless there is associated acute damage of heart or skeletal muscle or of liver, kidney, or brain. No consistent correlation has been found between the SGO-T activity and the temperature, white blood cell count, sedimentation rate, or C-reactive protein or blood fibrinogen levels.

Although marked elevations of SGO-T activity are seen in patients with hepatitis of varying etiology and moderate increases in some patients with cirrhosis and obstructive jaundice, the clinical setting is such that there is rarely any confusion with acute myocardial infarction in the differential diagnosis. The trauma to skeletal muscle during major surgery is frequently followed by minimal to moderate increase in SGO-T, SGP-T, and SLD activity for one to six days which mimics that following acute myocardial infarction, so that measurements of enzyme levels postoperatively do not constitute evidence for or against the presence of acute heart muscle cell injury. Metastatic liver cancer, moderately severe hemolytic crises, and mechanical injury to skeletal muscle are also associated with increased SGO-T activity.

Experimental and clinical myocardial infarction is followed by characteristic changes in the activity in SGO-T, SLD, and SGP-T, with the peak activity occurring within 12 to 24 hours and falling to or toward normal within two to five days. The height and duration of elevated SGO-T activity is roughly proportional to the amount of myocardial necrosis. The SGO-T activity increases proportionately more than the SLD or SGP-T activity following acute human myocardial infarction. It is of interest that the SLD activity persists two to three days longer than SGO-T activity following acute myocardial infarction.

The SGO-T activity determination is useful as a test in helping the clinician to decide whether substernal pain associated with an equivocal electrocardiographic picture is due to myocardial infarction. If transaminase values are known, in many instances it may be decided whether or not acute heart muscle cell damage has occurred when chest pain develops in the presence of left bundle branch block, healed myocardial infarction, or infarction of electrocardiographic silent areas of the myocardium.

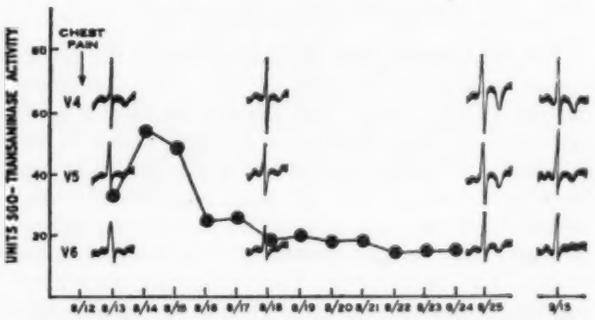

Fig. 5.—SGO-T level elevation in man who had angina.

Acute myocardial damage must be presumed to be present in patients with chest pain and equivocal electrocardiographic changes and who have elevation of SGO-T activity in the absence of known active liver disease. Further study is needed to evaluate the usefulness of SLD activity in such situations, and it must be remembered that minimal hemolysis will increase SLD activity.

The SGO-T activity will usually help distinguish acute pericarditis and pulmonary infarction from acute myocardial infarction, since SGO-T is uncommonly and only slightly and irregularly elevated following acute pericarditis and pulmonary infarction but rises promptly and follows a characteristic curve after acute myocardial infarction. Further study is needed to evaluate the significance of alterations of SGO-T activity in acute rheumatic carditis. The fact that infarcted heart muscle may contain one-fiftieth the GO-T, GP-T and LD activity of normal heart muscle suggests that the increased levels in the serum after myocardial infarction result from the release of these enzymes from the damaged heart muscle cells in excess of that which the body can destroy or excrete (fig. 1). Deviations in various enzyme elevations following tissue damage are not solely explicable on the basis of a simple release into the blood stream, and other mechanisms as yet unknown need to be elucidated.

Other enzymes present in heart muscle in high concentration may prove to be more significant and more regularly elevated and remain so for a longer period of time than either SGO-T or SLD. It is obvious that continued study of other enzyme systems of many tissues or of tumors may provide useful information both with regard to diagnosis and changes in tissue cell metabolism.

The activity in the serum of phosphohexoisomerase was increased in 16 of 18 patients after acute myocardial infarction and that of malic dehydrogenase in 17 of 18. The measurement of the activity of malic dehydrogenase, however, was admitted by the authors [9] not to be specific, and until the technique is stabilized and more results are available, the usefulness of these enzymes in the diagnosis of acute myocardial infarction is not established.

Nonspecific Phase-Reactants

The nonspecific phase-reactants include the erythrocyte sedimentation rate (ESR), the C-reactive protein (CRP) level, and plasma fibrinogen level and have all been studied as diagnostic aids in the diagnosis of acute myocardial infarction.[10] It has long been known that the ESR becomes elevated within 12 to 24 hours after acute myocardial infarction and may remain elevated for as long as seven weeks. The increase in ESR following infectious diseases or any disease associated with inflammation is a well-known fact. However, all of these phase-reactants are positive within the first three weeks in 90 to 98% of patients sustaining acute myocardial infarction.

As intimated above, the CRP level and ESR and plasma fibrinogen level may be positive in infectious diseases as mild as an acute upper respiratory infection, in gastrointestinal diseases which are complicated by infection, in acute gout, and in neoplastic diseases, as well as being altered by the mere presence of severe congestive heart failure. They are also strongly positive following pulmonary infarction and, of course, in pericarditis and acute rheumatic fever and rheumatoid arthritis and other collagen diseases.

Recent reports have shown that in almost 100% of patients sustaining an acute transmural myocardial infarction, the CRP level is positive after the third day.[11] The test for CRP remains positive for as long as three to seven weeks, although it is usually elevated for only two weeks in the absence of complications. Certainly the CRP level returns to normal before the ESR in most instances. The CRP test has proved to be negative in patients with acute coronary insufficiency, whereas the sedimentation rate may be elevated in some instances. These tests have the advantage of simplicity and adaptability to most laboratories but must be evaluated carefully because of their lack of specificity and abnormal values in a wide range of disease states.

Knowledge of the CRP level is of particular value when blood samples are not obtained within the first four days following myocardial infarction, since CRP values remain abnormal much longer than do the SGO-T values. The investigators who have studied CRP have stated that the test may uncover small infarctions when the transaminase activity is normal. However, such findings must be carefully evaluated in the light of the nonspecificity of this reaction.

115 E. 61st St. (21).

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SIGNIFICANCE OF CERTAIN EARLY CHANGES IN THE T WAVE IN CORONARY DISEASE

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The electrocardiogram is useful in the diagnosis and management of coronary artery disease. Interest is generally centered on the S-T segment and the T wave, but the QRS complex sometimes shows pronounced changes, and the vectorcardiogram may reveal mild and early alterations in the QRS loop in its various projections. Close inspection of the S-T segment and T wave reveals many subtle changes. These data, properly integrated with all the clinical data, are valuable, but to rely on them alone is to treat the electrocardiogram rather than the patient. Continued study of electrocardiograms in the light of postmortem findings is to be encouraged.

The electrocardiogram is a useful adjunct to clinical cardiology when it is not isolated but is intelligently integrated with all the clinical data.[1] The able physician treats the patient and not his electrocardiogram. This objective datum, however, may no more be ignored than the report of a blood culture in a patient with fever. It is as reliable as the recording and the interpretation. The recording, unfortunately, is not always as dependable as it should be because of inadequately functioning electrocardiographs and careless technical assistants, who place the precordial electrodes in erroneous positions. Such negligence cannot be justified. Furthermore, erroneous interpretation of the electrocardiogram with inadequate integration with the clinical data results from insufficient knowledge and experience in electrocardiography. Although these problems can be rectified, they often remain neglected, with resultant improper care of the patient.

The electrocardiogram can be of considerable value in the diagnosis and management of coronary artery disease. Those who search for dogmatic rules for its applicability, however, will be disillusioned. They will employ it with least success and with predictable disappointment but, because of lack of knowledge, will offer unsound criticism of the procedure. The primary problem resides not in the electrocardiogram, if it is properly recorded, but in the limitations of the person interpreting its significance. The present state of knowledge is far from complete, but certain presently known principles can be of value to the clinician. Selected phases of these will be discussed in the following paragraphs to illustrate the advantages as well as the difficulties yet to be resolved in electrocardiography.

The practice has been to limit interest to the T wave and S-T segment when searching for mild and early cardiac disturbances of the coronary arteries, even though it is known that the initial

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electrocardiographic changes, i. e., QRS and temporal changes, can be pronounced, as in complete heart block or myocardial infarction. Furthermore, since the advent of spatial vectorcardiography, mild and early alterations in the order of depolarization (recorded by the QRS sÊ-loop) have become equally evident and important, because the manifested electrical events are recorded in greater detail than in conventional electrocardiography. In the conventionally recorded electrocardiogram, the S-T segment and T wave have proved most useful in disclosing slight changes. Surely, QRS, temporal,

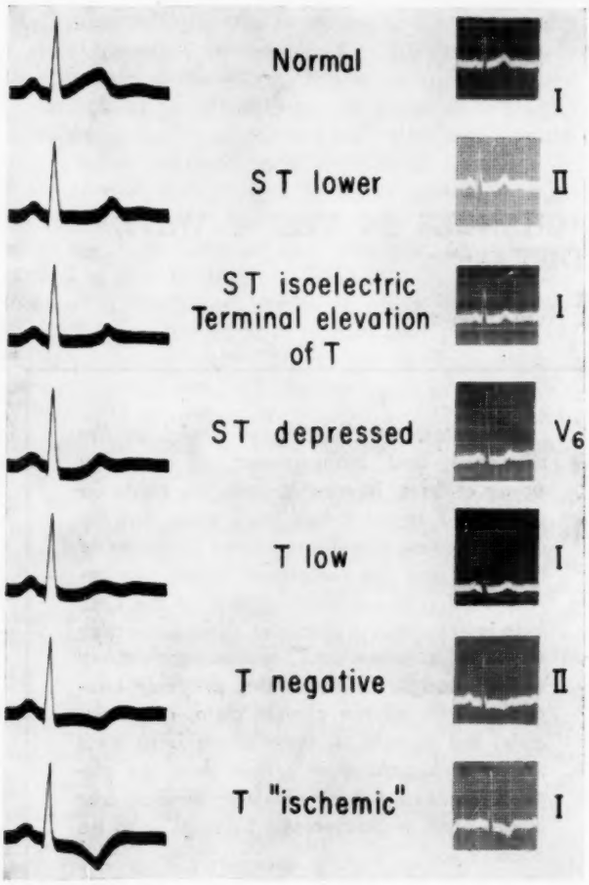

Fig. 1.—Electrocardiograms showing progressively more abnormal changes in T wave that may be encountered in association with coronary disease. Changes are diagrammatically illustrated at left of figure, and actual recordings are shown at right.

and other changes, when present, are to be fully exploited, but the present discussion will be limited to the S-T segment and T wave.

Some of the common, progressive changes in the S-T segment and T wave manifested by coronary disease are briefly summarized in figure 1. The normal T wave in leads I, V_5, and V_6, at least, is characterized by a gradual ascent to a summit, with more rapid descent to the isoelectric level. There is no true S-T segment, if by such a segment is meant absence of electric activity or absence of change in cardiac electric potential, with a resultant isopotential, horizontally recorded segment immediately after the QRS complex. Although small initially, the ascending limb of the T wave begins at the end of the QRS complex, and the earliest, but not quite isoelectric, portion is often considered to be the S-T segment. The beginning of the segment is the junction, J, and the end is some arbitrary point variously located within the ascending limb of the T wave by different observers without any absolutely satisfactory and generally accepted criteria having been established. Close inspection of the T wave of a normal person will disclose readily the characteristic configuration, which must be recognized for detection of significant early alterations produced by coronary disease.

The earliest electrocardiographic change that develops with coronary disease is lowering of the S-T segment or early portions of the ascending limb of the T wave (fig. 1). Initially, this limb of the T wave courses horizontally or ascends less rapidly (cardiac rates and other factors properly considered). This change, then, results in a configuration that resembles more the general concept of the S-T segment, but comparison with previous tracings will reveal the true nature of the change. With response of the patient to proper therapy, this portion of the S-T segment becomes elevated, to assume the previous normal configuration. The availability of previous recordings for comparison, the clinical data of coronary disease in the patient, and the reversion of the electrocardiographic changes after satisfactory therapy reveal the significance of these early and subtle alterations.

Since such early and mild changes occur in association with many factors other than coronary disease, such as normal physiological responses to smoking, eating, standing, or exposure to cold, their significance can be appreciated properly only in light of carefully and thoroughly collected clinical data. Confusion reflects poor clinical performance. Sometimes, clinical reexamination and a great deal of reflection are necessary before the proper connotation can finally be ascribed to such early changes in the T wave. To rationalize by considering slight changes unreliable or insignificant often indicates ignorance of clinical cardiology. All other causes of slight changes in the T wave must be properly eliminated before they can be considered the result of coronary disease.

As the coronary disease advances and the changes in the T wave indicate a progressively worse condition, more of the initial portion of this wave becomes lower and isoelectric (fig. 1). The T wave may be reduced in height, to result in the configuration of terminal elevation. The earlier portion of the T wave may then become depressed below the isoelectric line, even though the terminal portion remains positive (fig. 1).

If the clinical picture is typically that of angina pectoris, for example, then the significance of the changes in any of the foregoing configurations becomes evident. In instances in which interpretation of the clinical data is doubtful, the significance of these electrocardiographic changes can be demonstrated by the Master[2] two-step test (fig. 2), provided no contraindications exist and the proper precautions are observed. If the anginal symptoms are reproduced by exercise and further changes in the electrocardiogram appear, with reversion to the previous pattern after disappearance of the symptoms, then the evidence in favor of coronary disease is strong. If the patient is being treated temporarily for coronary disease while vigorous clinical study continues, subsequent serial electrocardiograms will disclose progression of changes in the T wave or reversion toward normal, if coronary disease is the etiological factor.

If the T waves indicate a progressively worse condition, they will become lower, isoelectric, negative, and, finally, typical of the "ischemic T wave" with coving (fig. 1). Only by careful clinical reevaluation, and, when possible, thorough postmortem study, with meticulous gross and microscopic examination of the heart in cooperation with the pathologist, can anyone accumulate the necessary experience for proper evaluation of early and subtle, as well as advanced, changes in the T wave in coronary diseases. Such postmortem study is to be rigorously encouraged.

Obviously, the electrocardiogram cannot be used alone for proper interpretation of the cause or clinical significance of coronary disease. Advanced disease of the coronary arteries may produce extensive alteration in the T waves or none at all, whereas mild disease may be associated with drastic changes in this wave. Furthermore, the alterations in the T wave may be similar for coronary disease produced by arteriosclerosis, periarteritis nodosa, thromboangiitis obliterans (Buerger's disease), or others, the clinical data providing the basis for differentiation. In addition, changes of these types may be indistinguishable from those produced by endocrine disturbances, acid-base imbalance, electrolyte imbalance and many other factors not known to be associated with either impairment of the circulation to the myocardium or myocardial ischemia. For this reason, changes in the T wave should be considered to be caused by ischemia only if the clinical data justify such a conclusion. Thus, the interpretation of ischemic T waves, so

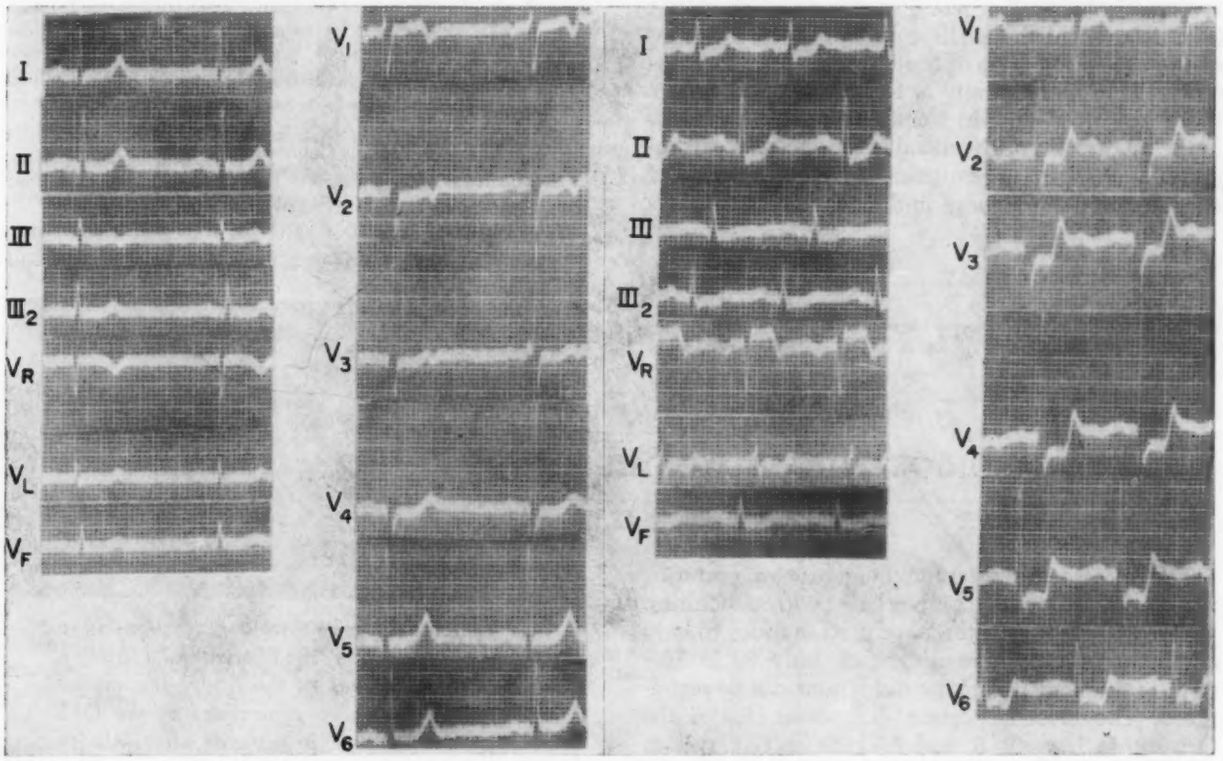

Fig. 2.—*Left*, electrocardiogram (before exercise) of 61-year-old man with arteriosclerotic heart disease and typical symptoms of angina pectoris. Configuration is essentially normal except for suspicious lowering of initial limb of T wave in standard limb leads and leads V_1 through V_6. *Right*, electrocardiogram (after exercise) of same patient. The Master two-step test produced typical attack of constricting chest pain at patient's ninth trip over steps. Note concomitant pronounced changes in S-T segment and T wave in all leads.

often made, should not be accepted literally unless all data indicate that myocardial ischemia is due to disease of the coronary arteries.

Thus, the electrocardiogram, when properly integrated with all the clinical data, can be of assistance in the diagnosis and management of disease of the coronary arteries. For most effective preventive and curative therapy, disease of the coronary arteries must be detected at its inception. The earlier the diagnosis is made, the more effective can be the role of the physician. It is imperative, therefore, to learn to identify the earliest and most subtle electrocardiographic changes that are produced by coronary disease. Anyone today can recognize sharply inverted ischemic T waves (fig. 1) as abnormal, but identification of the earliest alterations or lowering of the ascending limb of the T waves (fig. 1) is essential if proper therapy is to be instituted before more advanced and irreversible damage develops in the myocardium. Dismissal of early electrocardiographic changes as insignificant or unworthy of consideration in diagnosis and management displays prejudice or ignorance and is to be discouraged. On the other hand, improper use or "treatment" of the electrocardiogram rather than the patient is also untenable. The value of a properly recorded electrocardiogram in any clinical problem is directly related to the wisdom of its interpretation.

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VECTORCARDIOGRAPHIC DIAGNOSIS OF CORONARY ARTERY DISEASE

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Vectorcardiograms yield projections of a space-curve upon the horizontal, sagittal, and frontal planes of the body. The author examined the three projections of the QRS loop of this curve in patients after inferior myocardial infarction and pulmonary embolism. He concludes that an inferior infarct is manifested in increased duration and magnitude of the initial, superior QRS forces, clockwise inscription, and wide sweep of this loop in its frontal projection, and smallness or absence of terminal forces oriented to the right of or superiorly to the 0 point. Pulmonary embolism, on the other hand, was manifested in a broad clockwise inscription of the QRS loop in its frontal projection, with large rightward terminal forces and no slowness of inscription. Certain ratios computed from measurements on the vectorcardiograms emphasize the contrast between these two conditions.

The electrocardiographic diagnosis of posterior myocardial infarction is often beset with difficulties. If reasonably rigid criteria are used in order to help eliminate false-positive diagnoses, only 60 to 70% of the acute and 10% of the old lesions can be recognized. The most important diagnostic clue is the Q wave in leads 2, 3, and AV_f. Since Q waves in these leads occur in normal individuals and in a variety of pathological states, significant Q waves, i. e., those which indicate infarct, are recognized by their size and duration. The unreliability of these criteria becomes apparent with but little experience. Furthermore, in a significant number of patients with inferior infarction Q waves are not present in the specified leads, and the diagnosis, therefore, cannot be made by conventional electrocardiography. It is my purpose to discuss the vectorcardiographic diagnosis of posterior infarction, and especially its differentiation from the normal and from pulmonary embolism.

To distinguish normal electrocardiograms from those which indicate either inferior myocardial infarction or pulmonary embolism is often difficult

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or impossible. With vectorcardiography, however, this differential diagnosis has reached a degree of effectiveness never achieved, at least in my laboratory, with the electrocardiogram.

The double-cube reference system with positive polarity is used. The spatial loop is projected onto the horizontal, sagittal, and frontal planes of the body. Time markings equal 2.5 milliseconds; the narrow ends of the tear drops indicate direction of inscription of the loop. The largest loop is the QRS, the smaller ones are the P and T loops. I will confine my remarks to the QRS loop.

The Normal Vectorcardiogram

Each point on the horizontal loop is the resultant of the anterior-posterior and left-right components of the cardiac vector; sagittal plane points are the resultants of anterior-posterior and superior-inferior components; frontal plane points are the resultants of superior-inferior and left-right components of the cardiac vector. The normal loop is a smooth elliptical figure without sudden indentations or out-

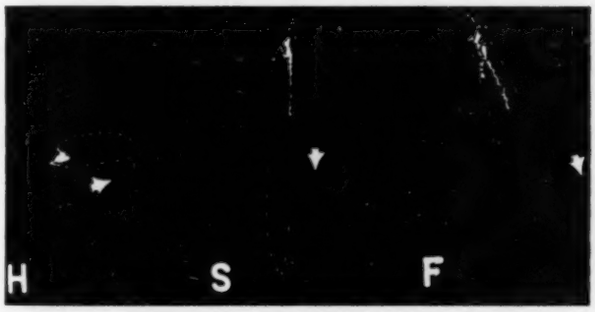

Fig. 1.—Normal vectorcardiogram. In this and following figures, H=horizontal plane projection, S=Sagittal plane projection, F=frontal plane projection. Arrows indicate direction of inscription of QRS loops. (See text.)

pocketings. Inscription of the horizontal projection is always counterclockwise and of the sagittal projection always clockwise. The inscription of the frontal projection is usually clockwise when vertical and counterclockwise when horizontal (fig. 1).

Useful measurements are the duration, magnitude, and sweep of the superiorly oriented initial forces, and the magnitude of the terminal rightward and superior forces.[1] The magnitude of the largest superior initial force is expressed as its ratio with the largest inferior vector of the body; it is called the superior-inferior ratio. The magnitudes of the largest terminal rightward and of the largest superior forces are expressed as ratios with the largest leftward and largest inferior vectors of the body respectively; these are called the rightward terminal appendage ratio and the superior terminal appendage ratio (fig. 2).

Inferior Myocardial Infarction

The vectorcardiogram displays five important signs of inferior infarct that are not visible or seen with difficulty in conventional electrocardiograms: the increased duration and magnitude of the initial, superior QRS forces, the clockwise inscription (the initial superior forces may be inscribed in a counterclockwise direction in the frontal plane when the infarct involves the lateral wall of the left ventricle) and wide sweep of these forces in the frontal plane, and the absence or smallness of terminal forces oriented to the right of or superiorly to the O point. These features are illustrated in figure 3, which

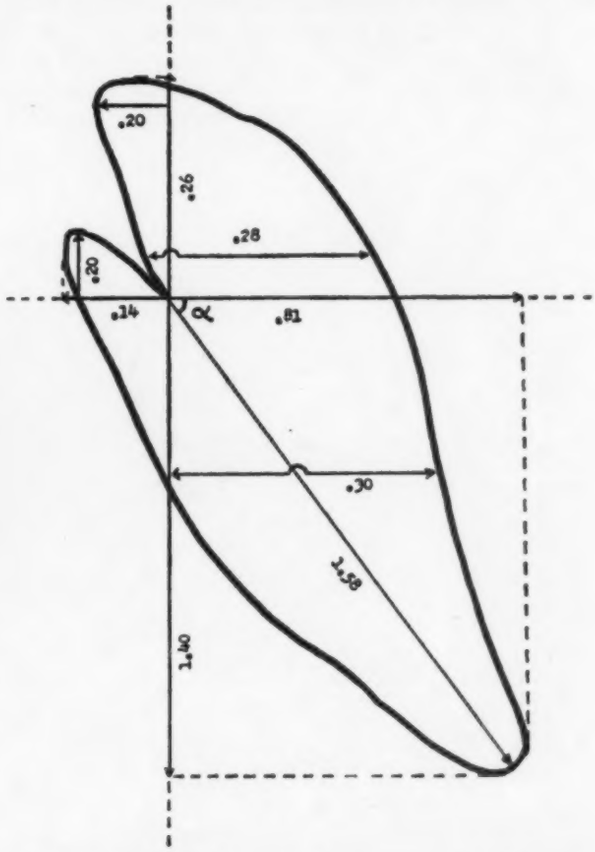

Fig. 2.—Diagram of frontal plane projection. QRS loop is counterclockwisely inscribed. See text for measurement of superior-inferior ratio and terminal appendage ratios.

also displays counterclockwise inscription of the sagittal plane QRS loop. Autopsy in this patient disclosed posterior myocardial infarction.

When the initial depolarization forces are at first inferior, as in figure 4, there are no Q waves in AV_f; the electrocardiographic diagnosis of infarct is impossible under these circumstances. The vectorcardiogram, however, reveals the characteristic diagnostic signs of posterior infarct as the trace quickly reverses its direction and describes large

superiorly oriented forces with a wide clockwise sweep in the frontal plane (fig. 4). A posterior infarct was demonstrated in this patient at autopsy.

The vectorcardiogram displayed in figure 5 is more complex than the previous ones, but the features of inferior infarct, though not striking, are discernible. Moreover, measurement of the initial and early vectors fell within the range established by us for posterior wall lesions, and the diagnosis of infarction was made. This patient was under treatment for congestive failure for two years, and though many electrocardiograms were taken, the diagnosis of infarct was not made. Autopsy revealed a posterior wall lesion.

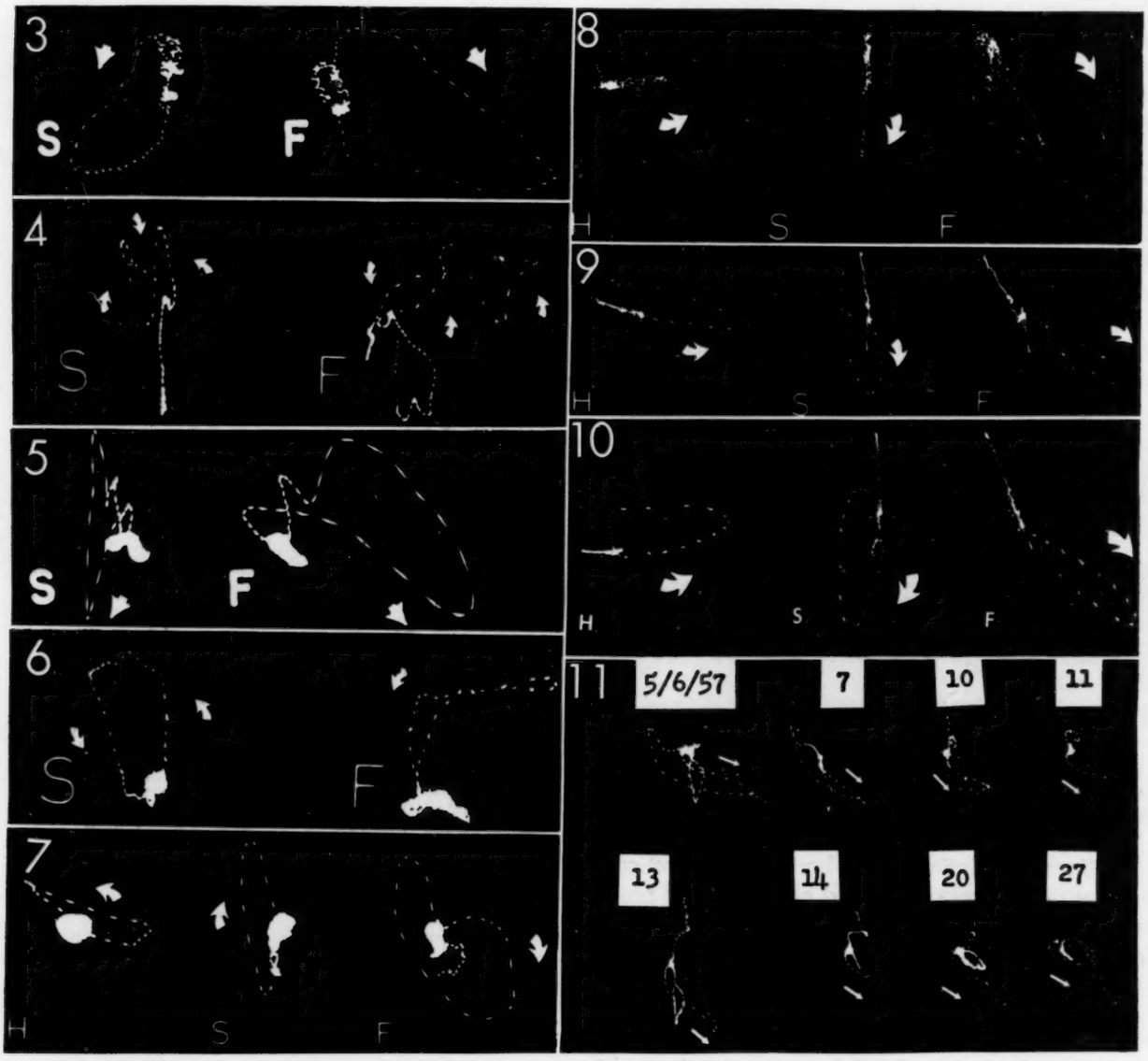

Fig. 3.—Sagittal and frontal plane projections in autopsy-proved case of posterior wall myocardial infarction. Initial superior forces are abnormally large and of long duration, they are clockwisely inscribed with wide sweep, and terminal vectors are not oriented to right and/or superiorly. Sagittal QRS loop is counterclockwisely inscribed. Fig. 4.—Saggittal and frontal plane projections in autopsy-proved case of posterior myocardial infarction. Initial forces are inferiorly oriented, but trace quickly reverses direction and describes features of inferior infarct. Fig. 5.—Sagittal and frontal plane projections in autopsy-proved case of posterior myocardial infarction. (See text.) Fig. 6.—Sagittal and frontal plane projections in autopsy-proved case of posterior myocardial infarction. Fig. 7.—Classic vectorcardiographic pattern of acute cor pulmonale. Autopsy disclosed normal heart and multiple pulmonary emboli. (See text.) Fig. 8.—Normal vectorcardiogram. Standardization: 1 mv.=3.5 in. (see text). Fig. 9.—From same case as figure 8, during pulmonary embolism. Standardization: 1 mv.=2 in. Note more horizontal position of frontal plane QRS loop and large terminal appendage oriented to right, posteriorly, and superiorly. Fig. 10.—Same case as in figures 8 and 9, after recovery. Standardization: 1 mv.=2 in. Frontal plane QRS loops is more vertical than in fig. 9, and terminal appendage has almost completely disappeared. Heavy linear trace at end of QRS loop is T loop. Fig. 11.—Frontal plane projections in same patient taken in May, 1957, on dates indicated by numerals. Acute pulmonary embolism prior to and on May 6, 1957. Bilateral femoral vein ligation done on May 6, 1957.

The next illustration (fig. 6) shows a bizarre loop, but the features of inferior myocardial infarction are strongly suggested. Autopsy disclosed a posterior wall lesion. The four vectorcardiograms shown in figures 3 through 6 display great variability in form, magnitude, and complexity, but all reveal the diagnostic signs of myocardial infarction.

Pulmonary Embolism

The difficulty in recognizing acute cor pulmonale in the electrocardiogram and of differentiating it from certain normal electrocardiograms and from inferior myocardial infarction is well known. I have observed in a number of cases a vectorcardiographic pattern in pulmonary embolism that I have not seen in any other condition or in normal individuals in over 2,500 cases studied.[2] Such a tracing is illustrated in figure 7 and displays the signs which I consider diagnostic of acute cor pulmonale: a rather horizontal but clockwisely inscribed frontal plane loop; small initial forces; large rightward, posterior, and superior (or inferior) terminal forces; and no slowness of inscription. The clinical diagnosis was pulmonary embolism, but the electrocardiograms were not diagnostic. Autopsy showed a normal heart and multiple pulmonary emboli.

TABLE 1.—*Terminal Appendage Ratios Before, During, and After Recovery from Pulmonary Embolism, from Vectorcardiograms Shown in Figures 8, 9, and 10*

	Before Pulmonary Embolism	After Pulmonary Embolism	Recovery
Right terminal appendage ratio....	0.04	0.25	0.11
Superior terminal appendage ratio.	0.05	0.59	0.23

Figures 8, 9, and 10 show the appearance and disappearance of the characteristic terminal appendage, as well as other features. The appearance and disappearance of the terminal appendage are clearly demonstrated by the terminal appendage ratios (table 1).

The frontal plane loops in another case of pulmonary embolism are illustrated in figure 11. Rapid changes occur with recovery from the acute cor pulmonale, with increased verticality of the loop as inscription changes from clockwise to counterclockwise, and diminution and final disappearance of the terminal appendage. The duration of the initial superior forces, the superior-inferior ratio, and the rightward and superior terminal appendage ratios in normal vectorcardiograms, inferior myocardial infarction, and pulmonary embolism, summarizing my experience to date, are shown in table 2.

TABLE 2.—*Various Measurements in Normal Vectorcardiograms and in Pulmonary Embolism and Inferior Myocardial Infarction*

	Pulmonary Embolism	Normal	Inferior Myocardial Infarction
Duration initial superior forces, sec. (mean)	0.018	0.014	0.034
Superior-inferior ratio, sec. (mean)..	0.17	0.07	0.78
Right terminal appendage ratio (mean)	0.42	0.17	0.07
Superior terminal appendage ratio (mean)	0.08	0.20	0.11

Summary

The vectorcardiogram is of great diagnostic value in inferior myocardial infarction. It clarifies to a degree not attained with the electrocardiogram the differentiation among normal findings and those in posterior myocardial infarction and pulmonary embolism.

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Etiology of Toxic Goiter.—The cause of thyrotoxicosis remains unexplained. It would certainly seem that it is related to overproduction of the thyrotropic hormone of the pituitary, and that the act of toxicity does not spring primarily from a disorder of function in the thyroid gland itself. The primary seat of the trouble may, however, occasionally be in the thyroid, as in the case of the solitary 'toxic adenoma', and in such patients a complete cure may be achieved. More often the cause or causes lie outside the thyroid gland, perhaps in the pituitary or other elements of the endocrine system, and these sources and situations are at present less vulnerable to successful attack and rational treatment, for the antithyroid drugs, radioiodine, and operation all act at the level of the thyroid gland itself. Heredity, sex, stress, diet, and a previously present goitre may each at times play a part. The incidence of toxic goitre is highest in individuals of unstable personality. It is said that no great statesman is known to have suffered from thyrotoxicosis, but it is certainly not uncommon in the highly cultured and artistic. Unstable personalities, if exposed to anxiety, responsibility, or emotional stress, are more likely to break down than others, and one way in which they may do so is by developing thyrotoxicosis. Our aim should be to reinstate the patient into thyroid balance. One cannot expect to alter a naturally excitable or unstable temperament.—V. Riddell, The Management of Thyrotoxicosis, *The British Journal of Surgery*, July, 1956.

PHYSIOLOGICAL RESPONSES DURING TOTAL BODY PERFUSION WITH A PUMP-OXYGENATOR

STUDIES IN ONE HUNDRED TWENTY PATIENTS UNDERGOING OPEN CARDIAC SURGERY

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In patients undergoing open cardiac surgery there are substantial differences in acid-base balance, preoperatively, between acyanotic and cyanotic patients. Metabolic studies on patients undergoing total body perfusion by means of a bubble oxygenator show the arterial pH values for all 84 acyanotic patients were within the range of normal at the termination of the bypass, and in 31 cyanotic patients the arterial pH remained at the control level—somewhat acidotic. Other physiological responses have been measured to achieve the goal of providing for the patient an optimum perfusion volume plus a margin of safety to allow for biological variations. This goal is obtained by monitoring each bypass procedure by means of a continuous recording of the patient's electroencephalogram and systemic blood pressure, and adjusting thereafter the perfusion rate to keep these variables normal or near normal.

The physiological responses, in 60 patients, to total body perfusion for open intracardiac surgery performed with use of a bubble oxygenator have been previously discussed.[1] Additional studies, including those on acid-base metabolism, blood glucose levels, variations in the serum potassium levels, and changes in 17-hydroxyketosteroid concentrations, have been made on the second group of 60 patients. The acid-base studies on the entire group of 120 patients are presented for more complete analysis. Blood glucose, serum potassium, and 17-hydroxyketosteroid concentrations have been measured to assess adrenal responses to this type of operative stress. These 120 patients varied in age and size from 8 weeks to 52 years and from 2,500 Gm. (5.5 lb.) to 80 kg. (176 lb.).

Methods

The pump-oxygenator system utilized for the total cardiopulmonary bypass is depicted in figure 1 and has been previously described.[2] The oxygenator utilized is of the large bubble principle with a helix reservoir and is constructed entirely of polyvinyl tubing, which is disposed of after each perfusion. The pump utilized in all these perfusions was the Sigmamotor unit (model T-6S for infants and small children and model T-M1 for larger children and adults) as modified for this use. All portions of the pump-oxygenator which come in contact with the patients' blood were sterilized by steam autoclaving.

The pump consists of a single explosion-proof electric motor which activates two pump-heads (arterial and venous), each equipped with an individual speed changer, all mounted on a single base. The artificial (large bubble) oxygenator has no moving parts, is sterilized by autoclaving, and is constructed entirely of polyvinyl plastic tubing which is discarded after each perfusion. From right to left in figure 1 may be noted the vertical mixing tube, the inclined debubbling chamber, and the helix reservoir immersed in a constant temperature waterbath. The venous blood is drained from the patient's caval cannulas by gravity flow into the plastic reservoir (in figure 1, attached to the leg of the pump table farthest to the right). From this reservoir it is circulated by the venous pump to the mixing tube. From the lower end of the helix, the oxygenated blood is returned through disposable filters to the patient's arterial system. The oxygen gas enters the venous blood directly through a nylon plastic diffusion plate at the base of the mixing tube. The venous blood carbon dioxide escapes with the excess oxygen during oxygenation. The coronary sinus return pump and plastic reservoir (in figure 1, attached to the table leg in the lower foreground), for returning to the oxygenator blood aspirated from the open heart, is seen on the lower level.

Arterial and venous blood samples were taken from the patient immediately before the onset of perfusion and just prior to its termination. One additional arterial sample was obtained about 15 minutes after the termination of the perfusion. Ad-

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ditional venous blood samples were taken 2 hours after the perfusion and on the following morning, about 18 hours later. No base was administered to any of these patients during their perfusion intervals, so that the data observed represent the patients' unmodified responses to the designated flow rates as well as the metabolic efficiency of the pump-oxygenator system. The patients' body temperatures were maintained at normal levels throughout the operative procedures.

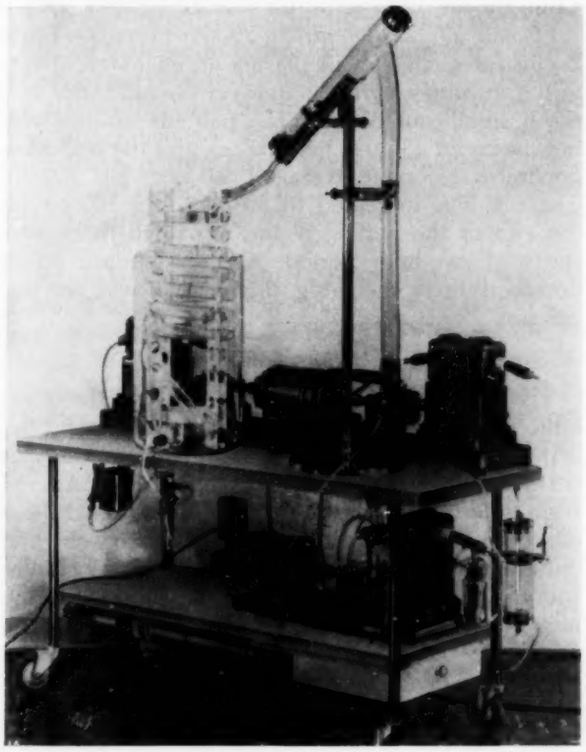

Fig. 1.—Helix reservoir pump oxygenator for direct vision intracardiac surgery.

All of the tests were done by standard laboratory techniques. The method of Silber and Porter [3] was used for the determination of 17, 21-dihydroxy-20-ketosteroid concentrations in the plasma. The plasma hemoglobin level was determined by use of the procedure described by Flink.[4] As previously described,[1] substantial differences were noted preoperatively between acyanotic and cyanotic patients; consequently, these two classes of patients are discussed separately.

Results

Acid-Base Responses.—The quantitative variations in acid-base responses during total body perfusion in the described patients are summarized in table 1. For all of these patients, a predetermined constant perfusion rate was used as indicated in the table. Data on 5 of these 120 patients were insufficient for inclusion in this table. It may be noted that the mean arterial pH in the 84 acyanotic patients at the end of the perfusions (mean duration 23.5 minutes) was in the normal range of 7.40 to 7.45 (table 1 and fig. 2). The control pH values taken immediately prior to the bypass for these patients were at alkaline levels due to intentional hyperventilation during the dissection phases of the operative procedure.

Patients with substantial right-to-left shunts are frequently in a state of metabolic acidosis [5]; this, it is not surprising to find that their control pH values indicate a somewhat acid state. However, they remained essentially unchanged (table 1) throughout the perfusions, which had a mean duration of 36.5 minutes. Figure 2 illustrates the data graphically. It is noteworthy that these same patients had normal blood pH values (fig. 2) the day after surgery. This observation was confirmation of the anatomic and physiological correction of the lesions.

In all patients, arterial plasma bicarbonate concentrations after perfusion were less than the control values; however, no significant differences in the plasma bicarbonate contents were apparent in the final arterial samples of the acyanotic patients, whose flow rates varied from 30 to 55 cc. per kilogram of body weight per minute (table 1). For the acyanotic patients these base deficits averaged 6.6 mM. per liter, while the mean value for the cyanotic group was 2.9 mM. per liter. In the acyanotic patients, this deficit was largely due to the addition and mixing of priming blood from the oxygenator reservoir, which had a mean bicarbonate level of 4.0 mM. per liter less than the patient control values. However, in the cyanotic patients the perfusion reservoir averaged 3.4 mM. per liter more bicarbonate than the patient control values.

TABLE 1.—*Acid-Base Responses to Total Body Perfusion During Use of Bubble Oxygenator*

Perfusion Rate, Cc./Kg./Min.	Patients, No.	Control Artery		Control Reservoir		Final Artery	
		Mean pH	Plasma Bicarbonate Concentration, mM./Liter, at pH 7.4	Mean pH	Plasma Bicarbonate Concentration, mM./Liter, at pH 7.4	Mean pH	Plasma Bicarbonate Concentration, mM./Liter, at pH 7.4
Acyanotics							
30-35	28	7.50	22.9	7.51	18.6	7.40	15.6
35-40	34	7.56	23.7	7.54	19.4	7.41	15.7
40-45	10	7.52	22.8	7.52	19.9	7.42	15.6
50-55	12	7.50	22.7	7.50	19.1	7.45	16.5
Cyanotics							
25-30	8	7.34	13.0	7.49	19.6	7.36	13.0
30-35	7	7.38	16.1	7.53	21.9	7.37	14.7
35-40	7	7.42	20.4	7.47	19.3	7.33	11.4
40-45	5	7.33	14.1	7.43	15.1	7.42	11.7
45-50	4	7.35	15.2	7.48	19.0	7.35	14.2

Serum Potassium Levels.—Serum potassium levels (fig. 2) in acyanotic patients tended to decrease during perfusions; a sharp decrease was seen in potassium content of arterial samples taken 15 minutes after the perfusion. In several patients, this value fell to levels below 2 mEq. per liter. Within two hours after the perfusion and without additional treatment of the patient, the serum potassium level

had returned to its normal range. The potassium levels in the cyanotic patients tended to increase during the perfusion but decreased to lower levels in the immediate postoperative period as did the levels in the acyanotic patients. All patients received small amounts of potassium in their parenterally given fluids (Meads 48 solution, containing 20 mEq. potassium per liter) after surgery, and this, in part,

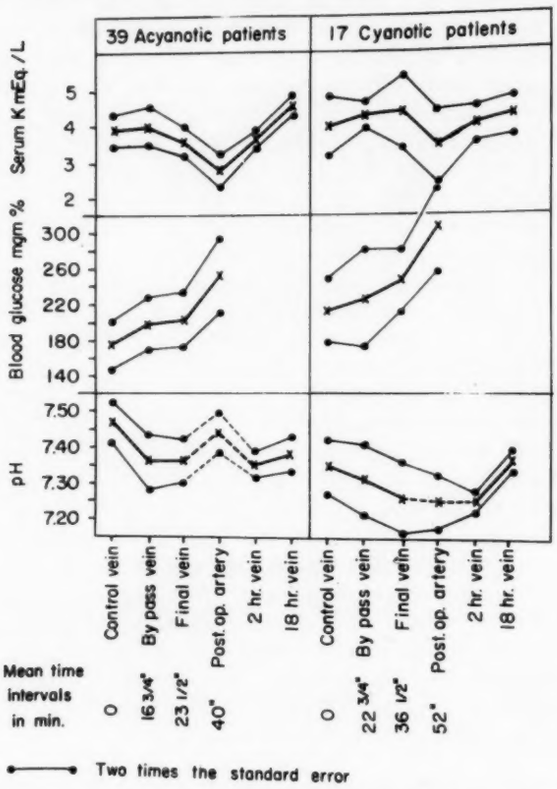

Fig. 2.—Variations in serum potassium and glucose levels and blood pH in response to total body perfusion.

is reflected in the normal potassium values 18 hours after the bypass. As shown in figure 2, the time of maximum fall in the serum potassium levels coincides with that of the peak levels measured for blood glucose.

Blood Glucose Levels.—During the procedure, a slow continuous drip of 5% dextrose in water has been maintained in these patients for administration of anesthetics and other medicaments. We have preferred to use glucose instead of saline solution for this purpose to obviate excessive administration of sodium chloride to these patients. This practice, in part, accounts for the elevated glucose levels seen in the control blood samples of these patients. However, after the onset of the perfusion, no exogenous glucose was given; consequently, the elevations in the blood glucose levels during the perfusion are intrinsic to the patient and doubtlessly related to adrenergic stimulation of glycogenolysis. During the perfusions, the blood glucose value in every patient increased more than 70 mg. per 100 cc. above the control level.

Plasma Hemoglobin Levels.—The plasma hemoglobin levels observed in these patients immediately after the perfusion were 0 to 25 mg. per 100 cc. in 37 patients, 25 to 50 mg. in 56, 50 to 75 mg. in 13, 75 to 100 mg. in 10, and 100 to 130 mg. in 4. The highest value was 128 mg. per 100 cc. The mean value for the 120 perfusions was 41 mg. per 100 cc.

Plasma 17, 21-Dihydroxy-20-ketosteroids.—Table 2 illustrates changes in plasma adrenal steroid values. The values increased in every circumstance, but not a significant degree. The patients' control values averaged 23 mcg. per 100 cc., and the perfusion apparatus reservoir averaged 30 mcg. per 100 cc. These values increased to 36 mcg. per 100 cc. by the end of the perfusion and remained there over the next two-hour period. As the standard errors demonstrate in the table, this change was not significant.

Comment

The mean arterial pH values in all of the acyanotic patients were within the normal range at the conclusion of the bypass, and in the cyanotic patients these values were not significantly altered from their control levels. It is emphasized that these observed responses in acid-base balance were the patients' own, since no exogenous base was administered. They are, then, an objective measure of the metabolic efficiency of respiratory gas exchange in this large bubble oxygenator wherein the venous blood is filmed directly upon the surface of the oxygen sphere.

In all patients, there was a decrease observed in the plasma bicarbonate levels during the perfusion interval. In the acyanotic patients, a significant part of this decrease was due to dilution resulting from use of the priming blood of the perfusion apparatus, which always had a plasma bicarbonate concentration less than that of the patient. The cyanotic patients generally had plasma bicarbonate values somewhat less than that of the reservoir. In this circumstance, the effect of the reservoir tended to maintain the plasma bicarbonate levels and the pH's of the patients constant throughout the procedure.

TABLE 2.—*Adrenal Corticoid Responses to Total Body Perfusion*

	17 Hydroxycorticone, Mcg./100 Cc.	Standard Error
Control patient	23	±5
Control reservoir	30	±3
End of perfusion	36	±5
2 hr. later	36	±5

The normal daily variation in plasma bicarbonate concentration has been described as 4 mM. per liter.[6] Thus, the average variation of 6.6 mM. per liter in plasma bicarbonate seen in the acyanotic patients did not greatly exceed this norm. The mean bicarbonate depression of 2.9 mM. per liter in the cyanotic patients was somewhat less than this norm. This bicarbonate depression is primarily due to the

accumulation of fixed acids.[1] Bicarbonate depression of the degree seen in these patients with total bypass is not significantly different than that observed in patients undergoing such relatively minor procedures as herniorrhaphy and pyloromyotomy.[6]

Epinephrine stimulation alone is known to produce an accumulation of fixed acids,[7] and this factor may be the common denominator of the bicarbonate depression incident to general anesthesia and a variety of major surgical procedures. Further, the decrease of plasma bicarbonate observed in these patients was spontaneously and rapidly corrected in the immediate postoperative period provided the patients had reparable defects and their hearts were able to maintain an adequate perfusion to their bodies.

Serum potassium depression is known to occur as a result of major surgery[8] and in response to epinephrine stimulation,[9] but it will be elevated during anoxia.[10] The serum potassium levels in all of our acyanotic patients decreased during and immediately after the bypass. This decrease occurred in spite of minimal degrees of hemolysis incident to the perfusion techniques.

Serum potassium levels in the cyanotic patients tended to increase during the perfusion, which may suggest that some degree of hypoxia was taking place. These patients have an abundance of large bronchial vessels, which effectively shunt into the lungs and open heart a variable portion of the blood introduced into the systemic circuit of the patient. We have frequently observed that the open heart of the cyanotic patient has a greater quantity of blood within it during the perfusion than does that of the acyanotic individual. It is now apparent that the cyanotic patients, because of their greater bronchial collateral circulation, receive a less effective tissue perfusion per given volume of total blood flow than do the acyanotic patients. The lesser degree of plasma bicarbonate depression that the desaturated individuals exhibit in response to perfusion is due primarily to compensation by the higher levels of plasma bicarbonate donated from the perfusion apparatus reservoir. Since recognizing these factors, we have perfused the cyanotic patient at rates higher than those that we consider optimal for the acyanotic.

The changes in the serum potassium levels can be of special significance in reference to the potentiation of digitalis effect by hypokalemia.[11] The blood glucose elevations observed in these patients are increased by exogenous administration but also are increased significantly from endogenous sources. Epinephrine stimulation is known to cause an elevation in the blood sugar level by mobilization of the body glycogen stores, especially from the liver.[12] Hyperglycemia, hypokalemia, and lactacidemia[1] are three factors which appear in this study, all of which could be produced by epinephrine release. The acute drop of the serum potassium level after the perfusion is believed to represent the reformation of the liver glycogen and the consequent withdrawal of potassium from the serum.[13] The alterations in plasma adrenal steroid levels which we observed in response to perfusion were of the magnitude that have been described as resulting from general anesthesia alone.[14]

The subject of the optimum perfusion rates that may be used for total body perfusion during reparative intracardiac surgery has been a contentious one among surgeons and physiologists. From the biochemical data herein reported together with those previously recorded,[1] supplemented by the routine monitoring of electroencephalograms during the perfusion intervals and clinical observations upon the general responses of these patients as well as recent observation on prolonged canine perfusions,[15] more definite impressions can be formulated concerning desirable perfusion rates.

It would seem from the evidence at hand that there is no more "an optimal perfusion rate" that can be applied to all patients undergoing total cardiopulmonary bypass than there is an optimal dosage of penicillin applicable to all patients. Such factors as age of patient, cardiac reserve, type of lesion, duration of operation, method of collecting blood for replacement, type of oxygenator, and perhaps other as yet unappreciated factors are important in the determination of an answer to this question. Thus, at present, we prefer to monitor each patients during the particular perfusion, utilizing a continuous recording of the electroencephalogram and the systemic blood pressure and adjusting thereafter the perfusion rate to keep these variables normal or near normal. These perfusions, too, are then further analyzed by study of the metabolic and physiological data (pH value, plasma bicarbonate level, oxygen and carbon dioxide content, plasma hemoglobin level, and platelet count) obtained before, during, and after perfusion.

These data obtained from 375 patients who have now undergone total cardiopulmonary bypass for open heart surgery are summarized in the following plan which appears to offer good protection to the individual patient undergoing total body perfusion by means of the helix reservoir oxygenator and Sigmamotor pump. This equipment is calibrated prior to the bypass to deliver flows at the rate of 50 cc., 60 cc., and 75 cc. per kilogram of body weight per minute. For infants and patients with cyanotic heart disease such as the tetralogy of Fallot defects, these perfusion rates are increased to as high as 100 cc. per kilogram per minute. During the course of the perfusion the response of the individual to the particular flow rate at which he is being perfused is monitored both with direct pressure recordings via a polyethylene tube inserted into the systemic system via the internal mammary artery and by means of the continuously recorded electroencephalogram. When either tracing reveals an unsatisfactory appearance, the cause is sought for and corrected, e. g., an unsuspected patent ductus

arteriosus. In the absence of such an obvious leak, the volume flow is raised until an adequate perfusion is achieved as judged by a return of these variables to normal or near normal. As a consequence of these steps, it is uniformly possible to achieve an arterial pH at the conclusion of the run which will be 7.36 or higher, although the patient may have been on the bypass for as long as one and one-half hours. Furthermore, he can be shown to have maintained a satisfactory electroencephalogram throughout the duration of this period. And, as a somewhat more practical expression that the interval of total cardiopulmonary bypass has been well tolerated, even for prolonged periods of time, is the fact that in the last 40 consecutive cases so treated and including a wide variety of congenital and acquired intracardiac lesions, there has been only one postoperative death—a mortality risk of 2.5%. Although this low risk depends upon application of proper surgical techniques and postoperative care as well, continuing successes in open heart surgery can rarely be achieved unless the perfusion itself was adequate.

Summary and Conclusions

Metabolic studies on 120 patients undergoing total body perfusion by means of a bubble oxygenator during open intracardiac procedures have been made. The arterial pH values for all 84 acyanotic patients were within the range of normal at the termination of the bypass. In 31 cyanotic patients the arterial pH remained at the control level—somewhat acidotic. However, in these individuals, 18 hours after surgical repair, the preoperative acidotic states had been corrected to normal levels.

A depression of the patients' plasma bicarbonate levels after total body perfusion was observed in all cases, but that of the acyanotic patients was not significantly greater than the normal daily variation of 4 mM. per liter, while that of the cyanotic individuals was less than this figure. The observed bicarbonate depression was of no greater extent than has been observed in other surgical patients having relatively minor procedures.

Serum potassium levels in the acyanotic patients were seen to decline during the perfusions and to decrease markedly in the immediate postoperative period and then to return to normal levels within two hours. This is correlated with and doubtless the result of the observed elevations in the levels of glucose, of both endogenous and exogenous origin, in the blood. Adrenal steroid levels were measured in the plasma of these patients, but only slight elevations were noted.

On the basis of these studies, a plan for management of perfusion procedures has been outlined which has proved satisfactory as judged by a steadily decreasing risk for open heart surgery.

University Hospitals (14) (Dr. Lillehei).

The following persons from the University of Minnesota Medical School aided in this study: Dr. E. B. Brown of the Department of Physiology in interpreting the biochemical data, Dr. Ellis Benson of the Laboratory Division in the adrenal corticoid determinations, and Mr. Eugene Johnson of the Department of Biostatistics in the statistical interpretation of portions of the data.

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METASTATIC CANCER OF THE BREAST TREATED BY ADRENALECTOMY

EVALUATION AND THE FIVE-YEAR RESULTS

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Adrenalectomy was performed in 52 patients with metastatic mammary cancer. There were two postoperative deaths. Objective remissions of varying duration followed in 12 of 32 patients who had bilateral adrenalectomy alone and in 8 of 18 patients who also underwent oophorectomy. The extent of the lesions had little effect on the result, for two patients with metastases so extensive that one appeared moribund survived more than five years with great regression of the neoplasm. Experience led to four criteria for selecting patients most likely to be helped by adrenalectomy: age between 40 and 65 years, indications of slowness of neoplastic growth, a high titer of estrogenic substances in the urine, and a rather well-differentiated appearance of the tumor under the microscope. There was no evidence that simultaneous oophorectomy helped in women older than 54 years.

The results of clinical treatments of cancer customarily are appraised at the end of five years, and this period of time has elapsed since the introduction of adrenalectomy for advanced cancer of the breast.[1] This new surgical therapy has proved to have both theoretical and therapeutic significance. It was discovered in this study that there is a hormonal component originating in the adrenal glands which sustains and propagates the disease in certain types of mammary cancer. Surgical excision of the adrenal glands of patients maintained on cortisone therapy [2] has proved effective in inducing regression of mammary cancer in cases of these sorts. This paper will demonstrate that prolonged survival and profound regression of cancer can occur, after the removal of the adrenal glands, in women with far-advanced mammary cancer.

Materials and Methods

The first series of patients treated by an adrenalectomy, or by this operation combined with oophorectomy, consisted of 52 consecutive patients [3] presenting far-advanced mammary cancer during the 20 months from May, 1951, to December, 1952 (see table). With a single exception, all of these patients had been subjected to mastectomy at an earlier time, and all had extensive metastases when adrenalectomy was performed. Forty-two patients had been previously treated with radiation and hormones of various kinds for their metastatic lesions. Bilateral adrenalectomy alone was performed in 34 patients who were postmenopausal or who had had a cessation of menstruation induced either by external irradiation or by surgical removal of the ovaries. The combined procedure of adrenalectomy and oophorectomy was performed in the remaining 18 patients. The operative mortality in this series was 3.8%. There were two postoperative deaths; one patient died immediately after the operation and one three days later, leaving an effective total of 50 patients. Two of these 50 patients were males with metastatic cancer of the breast.

Assessment of remission was based on both subjective and objective evidence of improvement. Objective remission is measured by regression or disappearance of obvious and easily accessible lesions such as cutaneous tumors and intra-abdominal masses and also by x-ray evidence of calcification of osteolytic lesions, the healing of fractures, or disappearance of pulmonary lesions and pleural fluid. Subjective improvement is often equally remarkable, especially in the relief of bone pain, disappearance of respiratory symptoms, and return of a sense of well-being. Subjective and objective improvements are not always concomitant. In some of the patients who reported marked subjective improvement, there was no demonstrable regression of the lesions. In this study, remission of disease following adrenalectomy was assessed chiefly by measurable objective evidence of improvement.

Results of Treatment

Objective remissions of varying duration have occurred in 12 of 32 patients (37.5%) who were subjected to bilateral adrenalectomy alone and in 8 of 18 patients (44%) who were treated with the combined procedure of adrenalectomy and oophorectomy. The over-all objective remission in this series is therefore 40% (20 of a total of 50 patients).

From the Ben May Laboratory for Cancer Research, the University of Chicago.

Results of Adrenalectomy in Fifty-two Patients with Mammary Cancer (May, 1951, to December, 1952)

Case No.	Age	Menopausal Status	Time Since Mastectomy	Site of Metastases	Previous Treatment	Response to Previous Treatment	Response to Adrenalectomy		Period of Survival Since Adrenalectomy, Mo.
							Objective	Subjective	
1	46	Postmenopausal (radiation)	13 mo.	Extensive skeletal (skull, rib cages, spine, pelvis, and femur), (pathological fracture)	Testosterone (2½ mo.); Estrogen (3 mo.)	None	Recalcification of all osteolytic lesions; relief of hypercalcemia; healing of pathological fractures	Cessation of pain; ambulatory; working	68
2	52	Postmenopausal (radiation)	120 mo.	Skeletal; pulmonary; lymph nodes	Testosterone (3 mo.); radiation	None	Resorption of pleural fluid; sclerosis of osteolytic lesions	Relief of pain; relief of respiratory symptoms	8
3	47	Postmenopausal (radiation)	2 yr.	Extensive skeletal, scalp, cerebral	Testosterone (9 mo.)	Relief of pain	None	None	8
4	44	Postmenopausal (radiation)	5 yr.	Extensive skeletal; pleural and pulmonary; lymph nodes	Radiation	None	None	None	3
5	58	Postmenopausal (5 yr.)	10 mo.	Skeletal; pulmonary; skin	Estrogen	None	None	None	1
6†	38	Postmenopausal (surgical)	10 mo.	Pulmonary; skeletal (pathological fractures)	Radiation; testosterone (3 mo.)	None	...	...	3 days
7*	35	Premenopausal	Immediate	Recurrent inflammatory carcinoma, lymph nodes	...	...	None	None	3
8	56	Postmenopausal (16 yr.)	4 yr.	Skeletal; pleural; pulmonary	Radiation to chest; testosterone (12 mo.)	None	None	Relief of respiratory symptoms	9
9*	40	Postmenopausal (radiation)	§	Bilateral ulcerative lesions of breasts; pulmonary; lymph nodes	Testosterone (2 mo.)	None	None	None	6
10*	42	Premenopausal	2 yr.	Skeletal; pulmonary	Testosterone (1 mo.)	None	None	None	3
11	58	Postmenopausal (radiation)	44 mo.	Skeletal; cerebral	Testosterone (10 mo.)	Relief of pain		Relief of nausea vomiting	4
12	47	Postmenopausal (radiation)	17 mo.	Extensive skeletal; lymph nodes	Radiation; testosterone	Relief of pain		Relief of pain	4
13	48	Postmenopausal (surgical)	15 mo.	Extensive skeletal; hepatic; intraperitoneal	Radiation; testosterone	Relief of pain	Sclerosis of osteolytic lesions; regression of liver metastases; Relief of intestinal obstruction; disappearance of ascites	Relief of pain; relief of symptoms of intestinal obstruction	28
14	64	Postmenopausal (15 yr.)	3 yr.	Pleural; pulmonary	Testosterone (5 mo.)	None	None	Relief of respiratory symptoms	10
15	58	Postmenopausal (14 yr.)	4 yr.	Skeletal; soft tissue	Radiation; testosterone (6 mo.)	None	None	None	2
16	52	Postmenopausal	2 mo.	Brachial plexus; lymph nodes	Radiation; testosterone (5 mo.)	None	None	Relief of pain	14
17	56	Postmenopausal	2 yr.	Skeletal; brain	Radiation	None	None	None	7
18*	29	Premenopausal	3 mo.	Lymph nodes; brachial plexus; pulmonary	Radiation	None	None	None	7
19*	47	Premenopausal	4 yr.	Pulmonary	Testosterone	None	None	None	3
20*	39	Premenopausal	2½ yr.	Pleural; pulmonary	Testosterone (3 mo.)	None	Regression of pulmonary lesions and resorption of effusion	Relief of respiratory symptoms; ambulatory; working	12
21*	41	Postmenopausal (1 yr.)	6 yr.	Skeletal; pleural	Testosterone	None	Sclerosis of osteolytic lesions; resorption of pleural effusion	Relief of respiratory symptoms, ambulatory; working	66 (still living)
22	47	Postmenopausal (radiation)	6 yr.	Extensive skeletal (skull, pelvis, long bones, spine and thoracic cage)	Radiation; testosterone	Some relief of pain None	Recalcification of osteolytic lesions	Relief of pain	14
23*	48	Postmenopausal (radiation)	1 yr.	Extensive skeletal and pleural	Radiation; testosterone (6 mo.)	None	None	None	3
24	71	Postmenopausal (surgical)	4 yr.	Skeletal; local skin	Radiation; testosterone (1 yr.)	None	None	None	1
25	58	Postmenopausal (8 yr.)	32 mo.	Extensive skeletal (pathological fractures)	Testosterone	Relief of pain	Sclerosis of osteolytic lesions; healing of pathological fractures	Relief of pain; ambulatory; working	48
26*	38	Premenopausal	1 yr.	Extensive skeletal; lymph nodes	Testosterone	...	Sclerosis of osteolytic lesions	Relief of pain	16
27*	45	Premenopausal	11 yr.	Pulmonary; pleural with effusion	Radiation	None	Resorption of fluid	Relief of respiratory symptoms, ambulatory working	13
28	62	Postmenopausal	5 yr.	Skeletal; pulmonary; pleural	Testosterone (2 mo.)	None	None	None	3
29	52	Postmenopausal (radiation)	3 yr.	Skeletal; pulmonary; local ulceration	Radiation; testosterone (5 mo.)	None	Sclerosis of osteolytic lesions; healing of ulcer; regression of pulmonary lesions	Relief of pain; relief of respiratory symptoms	25
30	61	Postmenopausal (8 yr.)	1 yr.	Local recurrent inflammatory carcinoma; contralateral breast metastasis	...	...	Total regression of inflammatory carcinoma; regression of carcinoma in contralateral breast	Relief of pain	48
31	58	Postmenopausal (8 yr.)	6 yr.	Skeletal; brachial plexus; lymph nodes	...	...	None	Relief of pain	7
32*	47	Postmenopausal (2 yr.)	5 yr.	Skeletal; pleural effusion	Testosterone (8 mo.)	Relief of pain	Resorption of fluid; sclerosis of osteolytic lesions	Relief of pain; relief of respiratory symptoms; ambulatory	24

Results of Adrenalectomy in Fifty-two Patients with Mammary Cancer (May, 1951, to December, 1952)—Continued

Case No.	Age	Menopausal Status	Time Since Mastectomy	Site of Metastases	Previous Treatment	Response to Previous Treatment	Response to Adrenalectomy		Period of Survival Adrenalectomy, Mo.
							Objective	Subjective	
33*	59	Postmenopausal (9 yr.)	3 yr.	Inflammatory carcinoma; pulmonary	Radiation	None	None	None	2
34	42	Postmenopausal (radiation)	1 yr.	Extensive skeletal	Radiation; testosterone (3 mo.)	None	Ostelytic lesions static	Relief of pain	16
35	45	Postmenopausal (radiation)	20 mo.	Skeletal; pleural with effusion	Radiation; testosterone (3 mo.)	None	Ostelytic lesions static	Relief of pain	7
36	57	Postmenopausal (surgical)	11 mo.	Skeletal	...	...	None	None	5
37	44	Premenopausal	1 yr.	Skeletal; pulmonary; pleural	Radiation; testosterone	None	None	None	1
38	45	Postmenopausal (radiation)	1 yr.	Extensive skeletal; pulmonary; intracranial	Radiation; testosterone	Relief of pain; sclerosis of osteolytic lesions	Sclerosis of osteolytic lesions in skull	Relief of pain; disappearance of symptoms of increased intracranial pressure	11
39	47	Postmenopausal (surgical)	19 mo.	Extensive skeletal	Testosterone (10 mo.)	None	None	None	8
40	52	Postmenopausal (radiation)	2 yr.	Extensive skeletal	Radiation; testosterone	None	None	None	8
41*	42	Premenopausal	8 mo.	Extensive pulmonary	...	...	None	None	4
42*	50	Postmenopausal (radiation)	1 yr.	Extensive pulmonary	...	...	None	None	3
43	50	Postmenopausal (surgical)	3 mo.	Extensive skeletal; pulmonary	Radiation; testosterone	None	None	None	4
44*	43	Premenopausal	4 mo.	Extensive carcinoma, en cuirass; intracranial	...	...	Regression of cutaneous lesions and intracranial metastases	Disappearance of symptoms of increased intracranial pressure	12
45	45	Postmenopausal (surgical)	7 yr.	Extensive skeletal	Radiation; testosterone	Relief of pain	Sclerosis of osteolytic lesions	Relief of pain; ambulatory; working	37
46*	39	Pregnancy	55 mo.	Massive cutaneous metastases; pulmonary	...	...	None	None	6
47	42	Postmenopausal (radiation)	2 yr.	Extensive skeletal intracranial	Radiation; testosterone	Relief of pain	None	Relief of pain; decrease of intracranial symptoms	10
48*	31	Premenopausal	1 yr.	Extensive skeletal extensive liver	Radiation; testosterone	None	Marked decrease of size of liver	Relief of pain	7
49‡	51	...	2 yr.	Bilateral pleural	Estrogen; castration	None Resorption of fluid	Complete resorption of fluid	Relief of respiratory symptoms; ambulatory; working	53
50‡	54	...	2 yr.	Pulmonary	Orchiectomy; stilbestrol	None	Regression of pulmonary lesions	Relief of respiratory symptoms; ambulatory	7
51	48	Postmenopausal (radiation)	16 mo.	Pulmonary; pleural with effusion	Gold-198 intrapleurally; testosterone	None	Complete resorption of fluid	Relief of respiratory symptoms; ambulatory; working	42
52†	52	Postmenopausal	3 yr.	Skeletal; pulmonary	Testosterone; radiation	None	Immediate postoperative death		

* Adrenalectomy and oophorectomy were performed.
† Postoperative death.
‡ Carcinoma of male breast.
§ Patient did not have mastectomy.

Subjective improvement occurred in 29 (58%) of the 50 patients. The duration of remission ranged from 7 to 66 months. Prolonged survival has occurred in seven patients (14%) who lived from three years to 68 months, with one patient still alive 66 months after adrenalectomy and without any evidence of relapse (see figure). Twenty-one patients (42%) failed to respond to adrenalectomy.

Report of Cases

Case 1.—A woman, aged 46, first discovered a lump in her left breast in July, 1949. Radical mastectomy was performed on Dec. 9, 1949, and the operation was followed by irradiation therapy. Osseous metastases became evident in January, 1951, and the patient was treated with testosterone for two months with no relief. Instead, rapid progression of osseous metastases followed, and the patient became confined to bed in February, 1951, with multiple pathological fractures of the pubis, ischium, and pelvis. Ethinyl estradiol was administered after testosterone had failed to produce relief, and this too resulted in no beneficial effect. Hypercalcemia developed while the patient was bedridden with extensive osseous lesions. There had been a unilateral oophorectomy in 1930 for an ectopic pregnancy. Menstruation ceased after irradiation of the pelvis in February, 1951. Bilateral adrenalectomy was performed on May 7, 1951. There was steady improvement after the operation, with healing of all of the fractures. The patient became free from pain and was ambulatory and able to do housework until the early part of October, 1956, which was five and one-half years after adrenalectomy. Then she noticed pain in the right arm, and radiography of the right humerus showed osteolytic lesions. In November, 1956, she had a pathological fracture of the humerus. Her condition then became steadily worse, and she died in January, 1957, 68 months after the adrenalectomy. She was the first patient treated with adrenalectomy for mammary cancer.

Case 21.—A woman, aged 41, first discovered a lump in the right breast in 1942, and she was treated by a simple mastectomy with postoperative irradiation in the following month. Local recurrence in the mastectomy scar in 1946 was treated by x-ray and by surgical excision in 1948. In August, 1951, she developed severe chest pain with cough, dyspnea, orthopnea, and marked edema of the right arm.

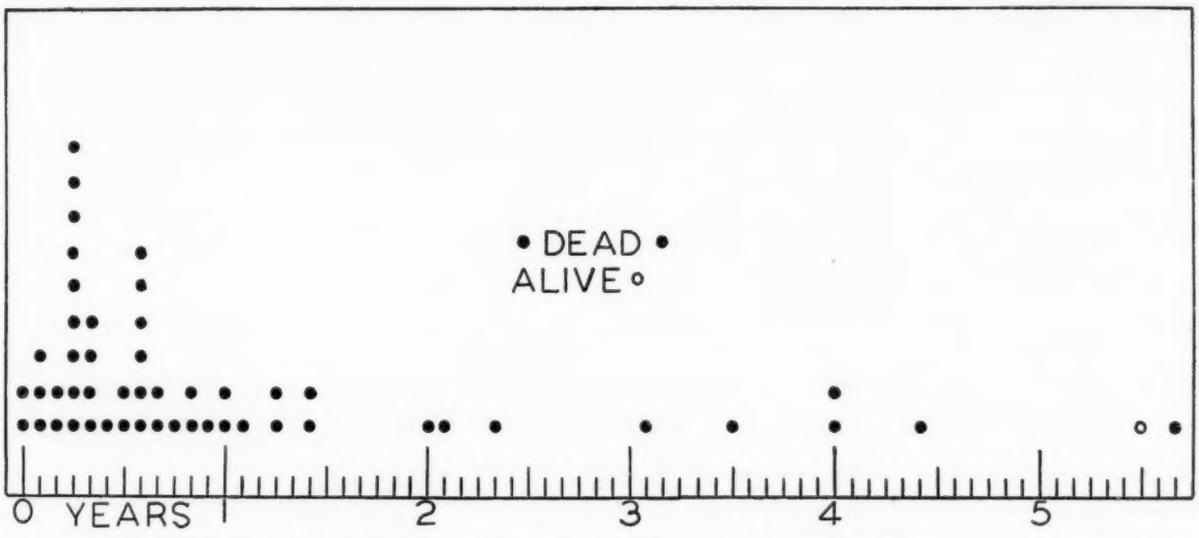
X-ray disclosed the presence of hydropneumothorax in the left side of the chest. Repeated thoracentesis was done at approximately weekly intervals. Neoplastic cells were found in the pleural fluid by cytological examination. The patient became bedridden. X-ray of the pelvis also showed numerous osteolytic lesions. Testosterone, 50 mg., was administered intramuscularly three times a week for three months with no improvement, but cessation of menstruation was induced by this hormone. Bilateral oophorectomy and adrenalectomy were performed on Dec. 19, 1951. There was almost immediate relief of the respiratory symptoms and resorption of the pleural fluid. Thoracentesis has not been required since the operation. Edema of the arm has disappeared. The osteolytic lesions in the ilium became sclerotic following the adrenalectomy. The patient is in excellent health five and one-half years after the operation.

Comment

The beneficial effects of bilateral adrenalectomy have been well established and confirmed by numerous investigators.[4] In our experience, regression of metastatic lesions of mammary cancer sometimes is profound, and prolonged survival following adrenalectomy has occurred in seven patients in the present series. This gratifying result is significant, since all of these patients were suffering from advanced mammary cancer and had failed to respond to several other types of therapy. Each of the seven patients was incapacitated before adrenalectomy was performed, and subsequently all of them were able to resume their normal physical activities. Maintained adequately with steroid substitution therapy, the adrenalectomized patients have a healthy appearance and are able to engage in all their usual pursuits. The hormonal maintenance of adrenalectomized patients is neither difficult nor perilous.

Shimkin and others [5] analyzed the survival of 374 patients with mammary cancer following the recurrence of the disease after mastectomy. It was found that the mean survival time of patients with local recurrence was 28 months, while patients with osseous metastases survived 22 months on the average, and those with generalized metastases lived 10 months. The mean survival of patients with generalized metastases in the present series treated by adrenalectomy is 27.6 months. There is no doubt that life was prolonged in most patients who had objective evidence of improvement after removal of the adrenal glands.

The two patients in the present series who survived, with great regression of the neoplasm, more than five years after adrenalectomy both had extensive metastases, and one of the patients appeared to be moribund. Therefore, the extent of the lesion is not of great consequence. The important factors in determining the effectiveness of adrenalectomy are that the tumor must be dependent on adrenal hormones and, specifically, that the adrenal glands must elaborate sufficient amounts of those steroids which maintain the growth of the neoplasm. When these conditions are fulfilled, the cancer undergoes atrophy after the adrenalectomy. A small autonomous tumor will not respond to adrenalectomy, whereas an extensive mammary cancer dependent on adrenal hormones involutes rapidly after the removal of the adrenal glands.



Periods of survival, after adrenalectomy, of 52 patients with metastatic mammary cancer.

We employ four criteria [6] which are helpful in the selection of patients for adrenalectomy. 1. The greatest relief has been observed in men or women 40 to 65 years of age. 2. A prolonged interval (more than one year) between mastectomy and manifestation of recurrence of the cancer often indicates that improvement will follow adrenalectomy. The rapidity of growth of a cancer indicates its degree of malignancy. The hormonal-dependent mammary cancers commonly are slow in their growth. The length of the postmastectomy interval of apparent freedom from cancer is a first approximation of the

growth rate of the neoplasm in the patient undergoing appraisal. 3. A titer of estrogenic substances in the urine above 15 I. U. daily is evidence of significant hormone production. 4. The hormonal-dependent mammary cancers are commonly rather well differentiated. Each of the seven patients in this series who had survival of three to five and one-half years after adrenalectomy had adenocarcinoma of the breast. Mammary adenocarcinoma is defined as a neoplasm composed largely or entirely of acini whose lining is one cell in thickness. Commonly the cancerous tubules contain milk in the lumina, and they are surrounded by myoepithelial cells.

It is known that there are dual sources of steroids which maintain mammary cancer in men and women. These are the gonads and the adrenal glands. We have found no evidence that the ovaries of women older than 54 years contribute to the maintenance of mammary cancer, and we do not perform oophorectomy in the treatment of cancer of the breast in women in this age group.

With regard to adrenalectomy in the treatment of mammary cancer, Stanford Cade [4a] has stated "In a proportion of cases both subjective and objective improvement has been achieved which has never been accomplished before by any other method of treatment." The results of the present series support this statement.

Summary

An evaluation of a series of 52 consecutive patients with metastatic mammary cancer who underwent adrenalectomy disclosed that significant remissions of varying lengths of time occurred in 20 patients. There were two postoperative deaths. Two patients survived more than five years, and one is alive with no clinical or laboratory evidence of relapse 66 months after the adrenalectomy.

The surgical excision of the adrenal glands in women or men with metastatic cancer of the breast has demonstrated that the sudden deprivation of the adrenal factor brought about a chemical change in the internal environment of the host and consequently produced a long continuing regression of the malignant neoplastic process. It is certain that hormone production by the adrenal glands is a component which maintains and propagates certain mammary cancers of the human male and female.

950 E. 59th St. (Dr. Huggins).

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The cortisone used in this study was provided by Merck & Co., Inc., Rahway, N. J.

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Schizophrenia.—There is a close relationship between mental disease and the autonomic nervous system. . . . Epinephrine plays a vital role in emergency reactions and anxiety states. Two oxidized derivatives of epinephrine, adrenochrome and adrenolutin, when administered to normal volunteers, produced changes in thought and mood, with or without perceptual changes, that in many ways resembled those found in early schizophrenia. Although direct evidence that these substances are present in the schizophrenic persons is lacking, there is a great deal of indirect evidence for this possibility, and enzyme systems that in vitro do effect the conversion of epinephrine to adrenochrome are present in vivo. It would be quite astonishing if this change were not found in vivo. Adrenochrome and adrenolutin are both antimitotic factors for L strain fibroblasts, and schizophrenic blood (which may contain these substances) is also toxic. . . . Epinephrine is converted by blood of schizophrenics into a fluorescent substance. Both substances produce catatonia and other changes when administered intraventricularly to cats. The hypothesis is developed that in schizophrenia both branches of the autonomic nervous system are overly active as a result of an overproduction of both acetylcholine and epinephrine. The changes suggested by this hypothesis are reviewed in the light of present information. It is suggested that this is a reasonable, unifying hypothesis that will prove useful in obtaining more information about schizophrenia.—A. Hoffer, M.D., Ph.D., Epinephrine Derivatives as Potential Schizophrenic Factors, *Journal of Clinical and Experimental Psychology and Quarterly Review of Psychiatry and Neurology*, January-March, 1957.

THE NEPHROTIC SYNDROME

CLINICAL OBSERVATIONS ON THERAPY WITH PREDNISONE AND OTHER STEROIDS

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The therapeutic effects of prednisone and hydrocortisone were studied in 20 patients who had the complete idiopathic nephrotic syndrome characterized by proteinuria, edema, hypoproteinemia, and hypercholesteremia. Three patients with proteinuria but only minimal hypoalbuminemia, hyperlipoidemia, and edema were also included. The most sensitive and satisfactory criterion for judging the day-to-day status of these patients and for recognizing remissions and exacerbations was the 24-hour output of urinary protein. No evidence of benefit was seen when the dosage of prednisone was insufficient to decrease the proteinuria. When the dosage was sufficient (generally 40 mg. of prednisone or 160 mg. of hydrocortisone daily), a decrease in proteinuria occurred in the majority of patients. This was usually manifest within 10 days, and after a month of treatment the dosage was gradually reduced. One to three years after the steroid therapy, 12 of the 20 typical patients are well, 4 are improved, and 4 are unimproved or dead. The treatment was ineffective in the three atypical patients without hypoalbuminemia and hyperlipoidemia and in one patient in whom the nephrotic syndrome was caused by renal amyloidosis.

A discussion of therapy of the nephrotic syndrome is complicated by the fact that this syndrome, characterized by massive proteinuria, edema, hypoproteinemia, and hyperlipoidemia, may occur during the course of many different diseases. Even after one has ruled out to the extent possible the recognized disease entities in which this syndrome sometimes occurs (diabetes mellitus, lupus erythematosus, amyloidosis, syphilis, malaria, and renal vein thrombosis), most cases of nephrotic syndrome are not satisfactorily classified. There may be a few patients in whom the nephrotic syndrome occurs during the course of a disease which apparently began as a typical attack of acute glomerulonephritis. Most give no history of such an onset and are classified as having "nephrosis" or "lipoid nephrosis," Longcope's type B nephritis,[1] Ellis' type 2 nephritis,[2] membranous glomerulonephritis,[3] subacute or chronic nephritis with edema, or the nephrotic or degenerative stage of chronic glomerular nephritis,[4] depending somewhat on whether the observer is internist, pediatrician, or pathologist. We have not attempted to subdivide the group of patients to be discussed here, after eliminating insofar as possible specific diseases, but have used the term idiopathic nephrotic syndrome to describe them all (although even this general classification is unsatisfactory since the nephrotic syndrome seen in lupus erythematosus and amyloidosis is also idiopathic). Some of this group of patients had normal renal function and blood pressure and only minimal microscopic hematuria. Others had renal insufficiency and more hematuria, which are findings usually considered characteristic of glomerulonephritis. Until the etiology of this disease or group of diseases is known and a better understanding of the natural history of the disease is attained, we prefer to include all of the patients described here in the category of idiopathic nephrotic syndrome, qualifying the term with a description of the features of each case rather than attempting to give names to what are largely arbitrary categories. We consider this term synonymous with the term nephrosis when nephrosis is used in this more general sense.

The present report is concerned with 25 patients with proteinuria of considerable magnitude treated and followed in the clinical center of the National Institutes of Health for periods of from 15 months to 3½ years up to June 1, 1957. Cases followed for shorter periods of time are not included. Twenty-two of these 25 patients had the complete nephrotic syndrome with serum albumin levels below 1.5 Gm. per 100 ml., edema, and hypercholesteremia. The remaining three patients had proteinuria of over 2 Gm. per day, but only minimal hypoalbuminemia, hyperlipoidemia, and edema. These three patients did not have all the manifestations usually included under the term nephrotic syndrome, and did have certain of the features which have in the past been considered characteristic of nephritis, but some of the latter features were also shared by the patients with the full-blown nephrotic syndrome. All of the patients except one child with malaria [5] were treated with prednisone, hydrocortisone, or both. A few pa-

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tients also received corticotropin (ACTH) or prednisolone. The major portion of the therapy was with prednisone.

The present study had several objectives. It has been known since 1950 that remissions can be obtained in many patients with the nephrotic syndrome with corticotropin and cortisone.[6] There is still disagreement as to the best therapeutic regimen with steroids and the extent to which they influence the long-term results. By trying different doses of steroids for varying periods of time, often in the same patient, we have arrived at a regimen which has produced satisfactory results in the majority of our patients. Another objective of the present study was the comprehensive evaluation of the relatively new steroid prednisone in the therapy of the nephrotic syndrome. We also hoped to determine whether response to steroid therapy could be correlated with age or with other clinical and laboratory findings.

Methods and Materials

Most of the patients were hospitalized throughout the periods of steroid administration and reevaluated at frequent intervals throughout the study. Table 1 presents a summary of each case studied. The numbers assigned to patients in table 1 are used throughout this report to designate the same patients.

On admission to the clinical center patients were placed on a diet containing approximately 200 mg. of sodium and 2 to 3 Gm. of potassium. This was continued throughout the period of steroid therapy. Prior to discharge the sodium allowance was liberalized in proportion to the patient's improvement. The diet was a well-balanced one, with the level of caloric and protein intake left largely to the patient's choice. It was necessary to restrict caloric consumption in several children because of excessive appetite and obesity developing during steroid therapy. Intermediate feedings and, in most adults, aluminum hydroxide were given during steroid therapy. Fluids ordinarily were given ad libitum. They were restricted as necessary in case of abnormally large intake and the development of hyponatremia. Children were given prophylactic penicillin, 250,000 to 500,000 units daily by mouth. This was given not only during steroid therapy but throughout the period of the disease and for six months to a year after remission. Antibiotics in adults, and antibiotics other than penicillin, were used only upon specific indication.

The patients were allowed to be up ad libitum. Blood pressure was determined each morning before the patient arose; when blood pressure was elevated determinations were made more frequently. Each patient was weighed before breakfast, after voiding. Complete 12-or-24-hour urine specimens were collected in bottles, usually containing a little formaldehyde solution, at least three times weekly. These were used for Addis counts and determinations of protein, electrolytes, creatinine, and aldosterone. No formaldehyde solution was added to specimens for aldosterone determination. Blood specimens were obtained weekly or semiweekly for determination of erythrocyte sedimentation rate, hematocrit, white blood cell count, eosinophil count, and serum proteins, lipids, electrolytes, creatinine, blood urea nitrogen, and other constituents as necessary. After a period of two weeks to two months of observa-

TABLE 1.—*Data on Twenty-five Patients on Steroid Therapy for Nephrotic Syndrome*

Case	Age, Yrs. (Sex)	Drug* Mg./24 Hr.	Laboratory Findings Before Therapy and at End of Study (June 1, 1957)† Total Protein Gm./100 Ml.	Albumin Gm./100 Ml.	Cholesterol Mg./100 Ml.	Creatinine Mg./100 Ml.	Urine Protein Gm./24 Hr.	RBC Millions/24 Hr.
Patients with severe edema and hypoalbuminemia								
1	1¾	Chloro-	5.1	0.8	432	0.4	1.8	6
	(F)	quine	**7.5**	**4.1**	**202**	**0.5**	**0**	**0**
2	2	Hy	3.8	0.2	724	0.7	1.5	4
	(M)	120	**6.9**	**3.9**	**186**	**0.5**	**0**	**1**
3	2½	Hy 100	3.2	0.7	858	1.8	8.0	25
	(M)	Pr 10						
4	2½	Pr 60, 40	4.5	0.4	1,040	0.6	4.0	54
	(F)		**6.6**	**3.8**	**199**	**0.4**	**0**	**0**
5	3½	Pr 40	3.9	0.5	1,045	0.4	5.0	20
	(M)		**6.8**	**3.9**	**224**	**0.4**	**0**	**1**
6	4¼	Pr 40	4.4	1.3	670	0.4	4.0	3
	(M)	Hy 160	**6.4**	**4.1**	**193**	**0.4**	**0**	**0**
7	4½	Pr 40	4.4	1.1	425	0.5	0.5	20
	(F)		**6.7**	**3.9**	**138**	**0.5**	**0**	**0**
8	6	Pr 40	3.9	0.9	352	1.2	5.0	300
	(M)							
9	7	Pr 40	3.8	0.8	1,033	1.2	5.0	10
	(M)							
10	7	Pr 80	3.0	0.4	1,080	1.2	6.0	3
	(F)		**5.3**	**2.9**	**334**	**0.6**	**2.0**	**3**
11	8	Pr 40	3.5	0.8	767	0.6	6.0	20
	(M)		**6.4**	**3.4**	**189**	**0.6**	**0.5**	**1**
12	9	Hy 80	4.1	1.2	518	0.5	1.2	80
	(M)		**6.9**	**3.8**	**176**	**0.6**	**0**	**0**
13	16	Hy 150, 80	3.9	1.1	679	0.5	3.0	50
	(F)	Pr 20	**6.7**	**3.8**	**186**	**0.7**	**0**	**0**
14	22	Pr 40, 80	4.2	0.7	472	0.6	3.0	25
	(F)		**6.2**	**2.2**	**165**	**0.7**	**1.5**	**3**
15	29	Pr 40, 80	3.4	0.7	1,800	2.1	12.0	17
	(M)		**6.4**	**3.6**	**252**	**1.0**	**0.7**	**0**
16	30	Hy 300	4.3	0.8	788	0.7	10.0	50
	(F)	ACTH 100 Pr 160	**5.0**	**1.7**	**522**	**1.4**	**10.0**	**30**
17	33	Pr 40	3.5	0.9	1,555	1.2	7.5	40
	(M)		**7.1**	**3.7**	**231**	**1.0**	**0**	**1**
18	41	Pr 40, 80	3.5	1.0	930	0.8	10.0	25
	(M)	Hy 160	**5.0**	**2.4**	**351**	**0.9**	**2.0**	**10**
19	44	Hy 300	4.3	1.5	559	0.7	7.5	15
	(M)	Pl 60 Pr 40	**6.7**	**3.5**	**214**	**0.8**	**0.5**	**2**
20	50	Pr 40	4.1	0.9	1,130	1.5	10.0	35
	(M)	Hy 160	**6.8**	**3.8**	**242**	**1.1**	**0**	**0**
21	54	Pr 40	3.7	0.9	746	1.3	12.0	0
	(M)							
22	61	Pr 40	3.2	0.8	700	1.3	12.0	15
	(M)		**5.2**	**2.3**	**240**	**1.1**	**5.0**	**15**
Patients without severe edema and hypoalbuminemia								
23	11	Pr 45	5.8	3.0	283	0.6	2.0	100
	(F)		**5.5**	**3.0**	**286**	**0.7**	**1.5**	**70**
24	30	Hy 300	5.5	2.8	294	0.9	7.5	250
	(M)	Pl 70	**6.9**	**4.1**	**240**	**1.0**	**1.5**	**20**
25	31	Pr 40	5.9	3.4	157	1.1	3.0	150
	(M)		**5.1**	**3.1**	**280**	**1.3**	**4.0**	**150**

* Highest dosage administered for at least 2 weeks, and dosage bringing about remission, if different from highest dose. Hy = hydrocortisone, Pr = prednisone, Pl = prednisolone, ACTH = adrenal corticotropic hormone.

† Figures in boldface type indicate laboratory findings at end of study.

tion in the hospital, 40 mg. of prednisone (or 150 to 200 mg. hydrocortisone) per day was administered orally in four divided doses. This was continued until the maximum change in levels of proteinuria or serum albumin occurred, in most cases for at least one month.

Response to Steroid Therapy

Pertinent data on the patients, including laboratory observations before therapy and at the end of the study, are recorded in table 1. Of the 22 cases of complete nephrotic syndrome, one child had quartan malaria and did not receive steroid therapy; this patient went into and remained in complete remission following chloroquine therapy for malaria.[5] One patient (case 21) had primary renal amyloi-

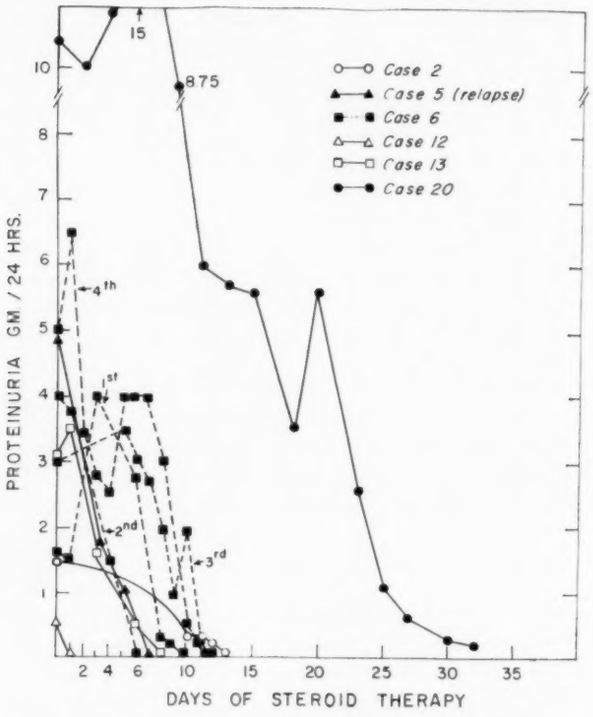

Fig. 1.—Decrease in proteinuria in patients in whom complete clearing of proteinuria occurred on steroid therapy. Response to treatment of several relapses in case 6 are included (designated 2nd, 3rd, 4th).

dosis. In this patient and the 20 remaining cases of complete nephrotic syndrome which are idiopathic, four types of response to steroid therapy were observed.

The first type, complete remission during steroid therapy with complete clearing of proteinuria, occurred in six patients (cases 2, 6, 7, 12, 13, and 20). Figure 1 represents graphically the effect of steroid therapy on proteinuria in this group of patients. A decrease in proteinuria occurred as early as the first day (case 12), but generally only after several days (as long as 10 days in case 20) and was often preceded by an initial increase in proteinuria. Once begun, the decrease in proteinuria proceeded rapidly so that the urine became protein-free within the first 48 hours in one patient (case 12) and in the second week of therapy in the rest with the exception of case 20, which required 30 days. Follow-

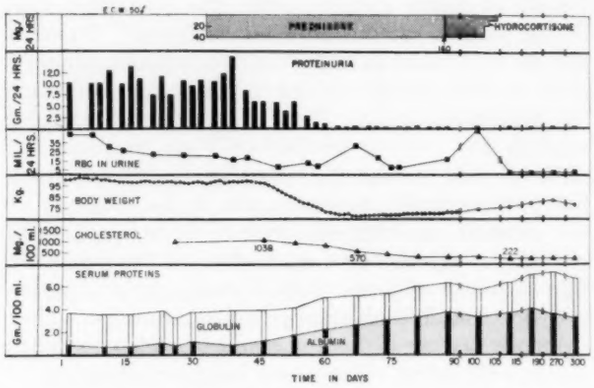

Fig. 2.—Response to steroid treatment in 50-year-old male (case 20).

ing the decrease in proteinuria, serum albumin began to rise, reaching normal levels within 30 days (except for case 20 which reached normal in 40 days). Serum cholesterol, often after an initial rise on starting steroid administration, fell gradually toward normal as serum albumin levels rose. Figure 2 (case 20) and figure 3 (case 6) illustrate complete remissions during steroid therapy. The response of case 20 was the slowest of the group while that of case 6 was more typical.

The second type of response was complete remission on steroid therapy except for residual proteinuria and this occurred in six patients (cases 4, 5, 11, 15, 17, and 19). The rather dramatic decrease

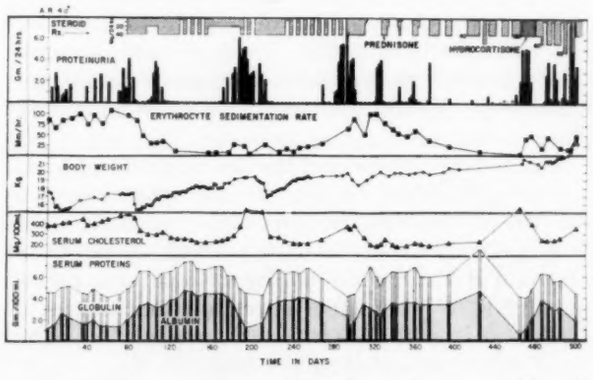

Fig. 3.—Response to steroid treatment in 4-year-old male (case 6).

in proteinuria, a pattern of response similar to that seen in the previous group, is illustrated in figure 4. In this group of patients the proteinuria, ranging from 5 to 10 Gm. per 24 hours, rapidly diminished (following an initial increase in four cases) until after two weeks of steroid administration a level of

0.5 to 4.0 Gm. per day (20 to 50% of pretreatment levels in individual patients) was reached. Serum albumin rose to normal levels within 30 days in four patients, but not until after about 60 days in cases

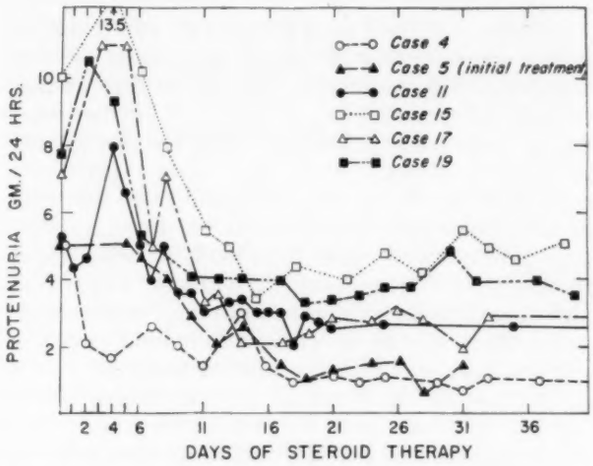

Fig. 4.—Decrease in proteinuria in patients in whom steroid therapy produced complete remission except for residual proteinuria.

11 and 20. Serum cholesterol, again after an initial rise at the onset of steroid therapy, fell gradually as the serum albumin rose. Figure 5 represents the course of case 4. The residual proteinuria in this case, as well as in cases 5 and 17, eventually disappeared without further treatment after the course of therapy was discontinued. In case 17 proteinuria finally disappeared 12 months after treatment. In cases 11, 15, and 19, proteinuria had diminished to less than 1 Gm. per 24 hours at the end of the study.

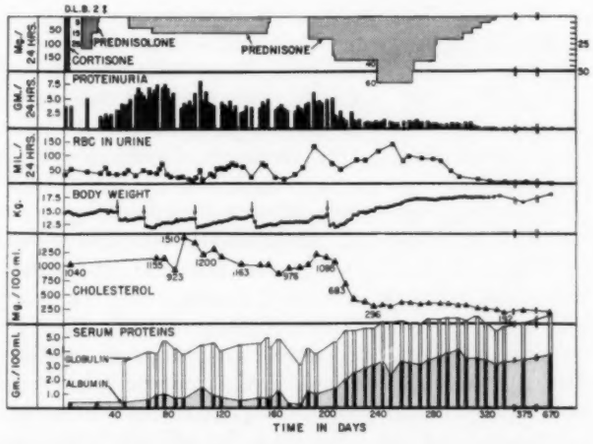

Fig. 5.—Response to steroid treatment in 2-year-old female (case 4).

The third type was partial remission with persistence of some albumin in the urine and some degree of hypoalbuminemia occurring in four patients (cases 10, 14, 18, and 22). Here the decrease in proteinuria and increase in serum albumin was less dramatic than in the other two groups and occurred either in the first 10 days of therapy (cases 17 and 22), or very gradually throughout the period of therapy and observation (case 14), or after steroid dosage was diminished (case 10). These four patients remained improved and edema-free but did not show any further improvement. Thus at the end of the study proteinuria remained above 1 Gm. daily in all, and serum proteins remained below normal. In patients with both complete and incomplete remissions (except case 10) a diuresis occurred during steroid administration coincident with an increase in serum albumin level.

The fourth type showed no change in proteinuria or serum proteins during steroid therapy and this occurred in the remaining five patients (cases 3, 8, 9, 16, and 21). Four of these patients had a diuresis on stopping or reducing steroid dosage although this was not associated with a decrease in proteinuria or an increase in serum albumin concentration. We have termed this a "symptomatic" diuresis to differentiate it from the diuresis occurring during a com-

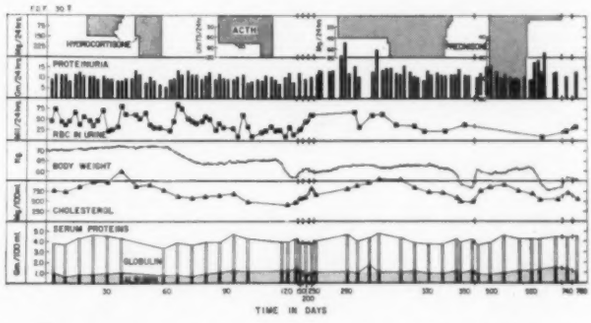

Fig. 6.—Response to steroid treatment in 30-year-old female (case 16).

plete or incomplete remission. Thus, although every patient became edema-free, we have not classified the occurrence of diuresis as a remission unless accompanied by diminution of proteinuria and increase in serum albumin. Figure 6 illustrates the course of one of these patients (case 16) in whom diuresis not accompanied by any change in serum proteins, serum cholesterol, or proteinuria occurred in withdrawal of steroid and adrenocorticotropic hormone treatment. One of the two adults who did not improve during steroid therapy (case 21) was shown to have renal amyloidosis and has died. The other (case 16), who at the time treatment was started was clinically indistinguishable from many who did improve, gradually developed progressive impairment of renal function and mild hypertension. The three children (cases 3, 8, and 9) who were unimproved during therapy had a progression of renal insufficiency (one with the onset of acute renal shutdown shortly after the course of steroid) and have all died.

Three patients (cases 23, 24, and 25) with proteinuria over 2 Gm. per 24 hours but without marked hypoalbuminemia or edema showed no significant diminution in proteinuria during steroid treatment. Case 24 subsequently had gradual diminution of proteinuria; the other two remained unchanged.

Table 2 gives a summary of the status as of June 1, 1957, of the 22 patients with nephrotic syndrome (including case 1 with quartan malaria and case 21 with renal amyloidosis) as well as the 3 patients with proteinuria without severe hypoalbuminemia. In the group of 20 cases of complete idiopathic nephrotic syndrome, 12 out of 20 patients are either well or have only minimal residual proteinuria (3 patients). Four patients are improved (clinically free of edema but still exhibit moderate proteinuria and hypoalbuminemia), and of the four patients who were unimproved by therapy, three are dead.

TABLE 2.—*Status of Twenty-five Patients with Proteinuria, June 1, 1957*

	Patients, No.	Case No.*	
		Children	Adults
Severe hypoalbuminemia			
Complete remission	10	1†	13‡
		2‡	17§
		4	20§
		5‡	
		6‡	
		7	
		12	
Remission with residual proteinuria	3	11‡	15‡§
			19
Partial remission	4	10§	14
			18
			22§
Unimproved	1		16
Dead	4	3§	21§‖
		8§	
		9§	
No severe hypoalbuminemia			
Improved	1		24
Unimproved	2	23	25§

* Numbers refer to cases in table 1.
† Quartan malaria with nephrotic syndrome.
‡ Relapses requiring further therapy.
§ These patients were thought to have some degree of renal insufficiency at the time of admission.
‖ Renal amyloidosis.

Judging from these studies, the quantitative determination of 24-hour urine protein is the most sensitive and satisfactory determination for following the day-to-day course of patients with the nephrotic syndrome, particularly for the recognition of remissions and exacerbations (fig. 2, 3, 5, and 6). When a patient is sent home in complete remission he (or the mother in the case of the children) has been asked to test the first morning specimen of urine with a protein precipitating agent. This rough test has served admirably to make frequent trips to the outpatient department unnecessary when the urine is protein-free and has enabled us to begin to follow any relapse closely from the day of onset of proteinuria. When a relapse occurred the onset of proteinuria was followed by a fall in serum albumin and in increase in serum lipids and erythrocyte sedimentation rate and often by an increase in body weight. At times the erythrocyte sedimentation rate was unreliable (e. g., in figure 3 on the 196th day and again on the 466th day the sedimentation rate was quite low during a time of severe relapse).

Management of Steroid Therapy

In three children (cases 4, 5, and 6) (fig. 3 and 5) it was observed that 20 mg. of prednisone per day was completely ineffective, whereas 40 mg. per day brought about complete remissions. Furthermore, two of these patients relapsed when the dosage was reduced to 20 mg. per day but again experienced remissions on 40 mg. (fig. 3). Largely on the basis of these observations we have chosen 40 mg. prednisone as the lowest initial dose likely to bring about remission in the majority of patients, adults and children, who are responsive to steroid, even though lower doses may be effective in individual patients. For example, a complete remission occurred in one child (case 12) on 80 mg. of hydrocortisone, and in one young adult (case 13) remissions occurred on 20 mg. prednisone per day and at another time on 80 mg. hydrocortisone per day. Support for the decision to initiate therapy in all patients with no more than 40 mg. prednisone has been the finding that in our series of patients larger doses have not been more effective, as detailed below.

Six patients (cases 4, 10, 14, 15, 16, and 17) who failed to obtain complete remissions while on 40 mg. prednisone per day have been treated with subsequent courses of 60 to 160 mg. prednisone daily. In none of these patients did it appear that the larger doses were definitely more effective than the 40 mg. level (fig. 5 and 6). Several of these patients (cases 4, 10, 14, 15, and 19) experienced further improvement after steroid therapy was discontinued, but this pattern was also observed in patients who did not receive further steroid therapy at the higher dosages. Although these larger doses of steroid were not effective when 40 mg. prednisone failed, we have continued to try a larger dose because there apparently have not been adequate trials of high doses of steroids in the nephrotic syndrome. The problem here has been to arrive at a compromise between the possible danger to the patient from prolonged high dosage of steroid and the possible benefit which we had hoped to see, but have so far not witnessed, with the increased dosage.

In summary, while there is variation in the dosage requirement from one patient to another, it appears that the majority of nephrotic patients who will respond to steroid therapy require about 40 mg. of prednisone per day. None of the present series of patients who did not respond favorably to this dosage were helped by a higher dosage. In most cases it has appeared to us that a given dosage of steroid is either completely ineffective or maximally effective.

When there was a favorable response as indicated by a decrease in proteinuria, the course of therapy was continued without reduction in dosage until no

further improvement in urine and serum protein levels occurred. This usually required three to five weeks of therapy and occasionally longer. In those patients in whom no decrease in proteinuria occurred, steroid dosage was either increased or discontinued after three weeks of treatment. When discontinuing prednisone therapy, the dosage usually was decreased by 50% per day down to 5 or 2.5 mg., continued at this level for several days, and then stopped. Relapses are discussed in the following section.

Two children, after the occurrence of complete remission (cases 2 and 12), developed upper respiratory infections associated with transitory proteinuria which cleared spontaneously without further therapy. Because of this observation patients have not been treated immediately for the initial recurrence of proteinuria unless it was severe and accompanied by a large decrease in serum albumin. Of the seven children and five adults in whom complete remissions or complete remission except for residual proteinuria occurred on steroid therapy, four children and two adults (cases 2, 5, 6, 11, 13, and 15) developed recurrent proteinuria which did not clear spontaneously. Relapses occurred within several days (case 6) to 30 months (case 2) after discontinuing therapy. Steroid therapy at the previously effective dosage level again produced remissions in all; four, however, have had further relapses and will be discussed in the section below.

Of the one child (case 10) and three adults (cases 14, 18, and 22) in whom partial remissions with subnormal serum albumin levels occurred, none have had a relapse, but all have continued to have some degree of proteinuria with moderate hypoalbuminemia.

As noted above, four patients with good responses to steroid therapy had relapses more than once after discontinuing therapy. Two of these patients (cases 13 and 15) had complete relapses with return of massive proteinuria, hypoalbuminemia, and hyperlipoidemia twice in a period of 12 to 18 months. One patient (case 5) had three relapses in 24 months. Re-treatment of each case according to the initially effective schedule again brought about remissions which have continued to the present time. There has so far been no evidence of decreasing responsiveness to steroid therapy. The fourth patient (case 6) has been a more serious problem. The course of this patient is shown in figure 3. Remissions were accomplished repeatedly in this patient by 40 mg. of prednisone or 160 mg. of cortisone daily. Relapses occurred each time that the steroid was discontinued or the dosage reduced. So far no completely satisfactory regimen of intermittent therapy has been found. Only with a dosage of 40 mg. of prednisone daily, or perhaps the same average dosage in the form of 80 mg. given alternately, with none for three-day periods, has remission been sustained.

Prednisone and hydrocortisone were compared in cases 6, 13, 16, 18, 19, and 24, as to their effectiveness in producing remission during relapses. Two patients (cases 17 and 20), who responded well initially to prednisone, also later received hydrocortisone in a study of steroid suppression of the skin inflammation produced by injections of serial dilutions of tuberculin according to methods previously described.[7] In no case did a patient respond well to therapy with 160 mg. of hydrocortisone when there had been a failure in the patient with 40 mg. of prednisone. Prednisolone and corticotropin have been used in too few cases to draw conclusions regarding their relative effectiveness. We conclude that prednisone and hydrocortisone were qualitatively similar in their effects on the nephrotic syndrome. Since the majority of these patients were treated with prednisone, our remarks are limited for the most part to this drug.

Factors Influencing Response to Steroid Therapy

Age.—In the small series of patients presented, the results of therapy in adults were not greatly different from those in children (table 2).

Hematuria.—Persistent microscopic hematuria was found in all of these patients with idiopathic nephrotic syndrome (table 1). When the number of red blood cells varied from several million to about 100 million per 24 hours (normal: less than 1 million per 24 hours), there appeared to be no correlation between degree of hematuria and result of therapy. Two patients (cases 12 and 16) both had hematuria ranging from 50 to 100 million red blood cells per 24 hours. One of them (case 12) had a complete remission on steroid therapy while the other (case 16) has had no improvement in the disease process with steroid therapy. Although the excretion of less than 100 million red blood cells per 24 hours did not ensure a favorable response to therapy, the four patients with hematuria well above this level—one patient with severe hypoalbuminemia (case 8) who occasionally had gross hematuria and the three patients (cases 23, 24, and 25) without severe hypoalbuminemia—all failed to respond well to steroids.

Casts.—All the patients listed in table 1 excreted an abnormal number of casts in the urine (more than 100,000 per 24 hours) at one time or another. All have had fatty casts and epithelial cells filled with lipid droplets (oval fat bodies). No consistent qualitative difference was detected between the types of casts in patients with different responses to steroid treatment, except that blood casts were seen in cases 3, 4, 8, 9, 23, 24, and 25 and only one of these (case 4) responded well to steroid therapy. The patients who responded well to steroid therapy (cases 2, 6, 7, 12, 13, and 20) excreted less than 500,000 casts per day. In three patients with eventual complete remission (cases 4, 5, and 17) counts of over 2 million casts per day were not uncommon. Of the four patients with an unfavorable course, two excreted the largest number of casts (over 10 million

per 24 hours in cases 8 and 16), while the other two patients (cases 3 and 9) had less than 500,000 casts per 24 hours. So it has not been possible to use the number of casts as a reliable prognostic aid in individual cases.

Hypertension.—The present studies do not allow any conclusions about the prognostic significance of elevated blood pressure since only one patient (case 8) had definite hypertension at the time of admission. This patient eventually died of renal insufficiency.

Renal Insufficiency.—Of the four children (cases 3, 8, 9, and 10) with impaired renal function at the time of admission, only one (case 10) had a partial remission and increase in renal function with steroid therapy. On the other hand, decreased renal function did not preclude a good response to steroid in several of the adults. Of the adults with severe hypoalbuminemia, cases 15, 17, 20, 21, and 22 were found to have some impairment of renal function. This was indicated by elevation of the blood urea nitrogen and decrease in renal clearances as well as the elevated creatinine level shown in table 1. Inulin clearances (milliliter per minute per 1.73 square meters of body surface) rose from 28.5 to 57 (case 15), 74 to 94 (case 17), 70 to 120 (case 20), and 47 to 76 (case 22) during steroid administration, and improvement in renal function has been maintained to date.

Hematocrit Level.—A number of patients, children and adults, in whom complete or incomplete remissions were obtained had at one time or another a hematocrit level as low as 35%. One patient in whom a partial remission occurred (case 10) had a hematocrit level of 30 on admission. Two children with more severe anemia, which became progressively worse, died (cases 3 and 9).

Failure of Previous Steroid Therapy.—Five patients (cases 3, 4, 5, 10, and 11) had had diuresis after 10-day courses of corticotropin or cortisone elsewhere, but had finally failed to respond favorably to further trials of short-term steroid therapy. One patient finished an ineffective 10-day course of 200 mg. of cortisone daily as she was admitted to the clinical center (case 4, fig. 5). All of these patients except in case 3 responded well to adequate steroid dosage in the present study. In case 3 it was impossible to ascertain whether the previous responses to short-term corticotropin therapy were due to "symptomatic" diuresis accompanying steroid withdrawal or whether a diminution in proteinuria actually occurred. We have not so far seen the development of steroid resistence in our own initially responsive patients who later had a relapse.

Complications and Side-effects of Steroid Therapy

All patients developed some degree of facial rounding, changes in fat deposition, and hirsutism (particularly children and females). Acne occurred in most cases but was quite variable. In some cases a papular erythematous rash occurred after discontinuing steroid therapy. Increased appetite, euphoria, and a feeling of nervous tension in the adults were noted commonly. Three adults (cases 16, 19, and 20) became paranoid; in each case the symptoms reached a climax after a decrease in therapy had occurred at the end of the course of treatment. Several patients complained of muscle cramps during therapy.

A mild elevation of blood pressure occurred in many of the patients while receiving prednisone or hydrocortisone; this disappeared after treatment was discontinued. One patient with preexisting renal insufficiency, anemia, and mild hypertension (case 3) developed severe hypertension and died while on a small dosage of prednisone. Only one other course of steroid was discontinued because of hypertension (prednisone, 80 mg. per day in case 10); this was later reinstituted without untoward results.

An elevation in blood urea nitrogen occurred in many cases during steroid therapy, presumably as a result of the raised urea load resulting from increased protein consumption as well as increased protein catabolism. Serum creatinine usually did not rise and glomerular filtration rate actually increased in the majority of cases. The upper limits of normal for serum creatinine in our laboratory appeared to be 1.0 mg. per 100 ml. in adults and 0.7 mg. per 100 ml. in children. One patient (case 8) with preexisting renal insufficiency and hematuria developed anuria about a week after prednisone had been reduced to a low level.

One patient (case 24) developed a bleeding duodenal ulcer requiring gastric resection five days after discontinuing a course of 70 mg. of prednisolone. Several other patients had mild gastrointestinal symptoms which did not persist. In one patient (case 22), there was an acute onset of chest pain and fever occurring at the end of steroid therapy. Subsequent x-rays showed evidence of emphysematous blebs surrounded by pulmonary infiltration. Although tuberculosis was suspected, no definite cause for the pulmonary infiltration was found. No other infections occurred during steroid therapy with the exception of a few viral upper respiratory tract infections.

Moderate chest pain and slight electrocardiogram changes interpreted as a possible myocardial infarction developed in case 18 after a week of prednisone therapy. Therapy was discontinued for two weeks and then resumed without further difficulty. No cases of severe osteoporosis or fractures occurred. Glycosuria was not noted except in the two cases (3 and 15) where it existed prior to steroid therapy. Eosinopenia and lymphocytopenia occurred in all cases during steroid therapy. Polymorphonuclear leukocytosis often occurred, particularly in children where levels above 20,000 white blood cells per cubic millimeter were sometimes reached.

Perhaps because of the restricted intake of sodium and the already maximal retention of sodium in most patients, no difference was noted in the effects of the various steroids on sodium retention or potassium excretion. Paracenteses were necessary in only one patient (case 4) in order to prevent recurrences of rectal prolapse. Serum sodium levels as low as 128 mEq. per liter were seen in many of the nephrotic patients. Since the lipid phase of serum contains little or no sodium, a sodium level expressed in milliequivalents per liter of total serum in patients with high triglyceride levels is lower than a sodium level in milliequivalents per liter of serum water.[8] However, in four children (cases 4, 5, 9, and 11) serum sodium levels fell during steroid therapy (to 114 mEq. per liter in case 4 and 120 mEq. per liter in the others). In each case this was associated with a fluid intake of at least 2,000 ml. per day and a gain in weight of about 1 to 1.5 kg. (2.2 to 3.5 lb.). Restriction of water intake resulted in a rise in serum sodium. We believe these were episodes of mild water intoxication resulting from the increased appetite and fluid intake due to steroid together with the extreme sodium restriction of the experimental diet.

Serum potassium levels remained normal in most cases. The patient who developed anuria had an elevated potassium level. One other patient (case 4) had potassium levels up to 7.2 mEq. per liter without known cause. Definitely low potassium levels were not observed in any patients. In general, the carbon dioxide content of the serum was normal and chloride was normal or reduced in proportion to sodium reduction. The complications of steroid therapy in the present study were similar to those reported elsewhere and it was not evident to us that complications during prednisone therapy differed appreciably in incidence or type from those seen during hydrocortisone therapy.

When the edematous patients were hospitalized and placed on a 200 mg. sodium diet no significant diuresis occurred in 11 patients (cases 2, 3, 4, 5, 6, 8, 10, 11, 13, 16, and 19) but a moderate to marked diuresis with loss in body weight of 5 to 13 kg. (11 to 28.7 lb.) occurred in four patients (cases 14, 15, 18, and 22). The remaining cases fell between these two extremes. All the edematous patients had hypoalbuminemia with serum albumin ranging from 0.2 to 1.5 Gm. per 100 ml. There was no correlation within this range between level of serum albumin and the occurrence or lack of occurrence of diuresis on a low-sodium diet. We have no data to suggest a reason for the differing degrees of sodium retention in these patients. Contrary to our expectations, aldosterone excretion in the few patients studied was not closely correlated with the degree of sodium retention. In fact, two edematous patients (cases 10 and 16) who failed to have diureses while receiving a 200 mg. sodium diet had urinary aldosterone levels of less than 5 mcg. per day (normal range 1 to 10).

Possible Etiological Factors

None of the patients was diabetic, though glucose and abnormal quantities of amino acids were observed in the urine of two patients (cases 3 and 15). Serologic tests for syphilis, Congo red tests, and examinations for the presence of lupus erythematosus cells were negative in all patients in whom these tests seemed to be indicated. None of the patients had evidence suggestive of renal vein or inferior cava thrombosis or of chronic urinary tract infections.

Among the children with severe hypoproteinemia, the renal disease was apparently due to quartan malaria in one (case 1). The disease was said to have been of insidious onset in two patients (cases 2 and 10). In case 9, the onset of edema followed by about three months an attack of measles from which the patient had never completely regained his strength. In the remaining eight patients, the symptoms of nephrosis were said to have followed some type of respiratory infection. This was in most cases an upper respiratory infection associated with coryza, cough, and sometimes gastrointestinal symptoms. One of these patients had tonsillitis with a temperature of 104 F (40 C) (case 7), and several others were known to have had fever; in the majority, the illness was thought to have been due to a virus infection. In the adults with severe hypoalbuminemia, the renal disease in one case (21) was associated with primary amyloidosis diagnosed by biopsy. In six cases (14, 15, 16, 18, 20, and 22) the disease was described as insidious in onset. In case 19, the onset of the disease occurred during desensitization injections for hay fever. In two patients (cases 13 and 17) the onset of edema was preceded by a respiratory infection with sore throat and bronchitis. In two of the three patients without severe hypoproteinemia (cases 23 and 25) there was a history of antecedent respiratory infection with fever. The other of these patients (case 24) had had a severe cold followed by proteinuria eight years before, but an insidious onset of the present episode of renal disease so far as is known. Cultures and determinations of antistreptococcin titers were carried out in cases where specific infections were suspected. No beta-hemolytic streptococci or pneumococci, and no antistreptococcin titers above 1:50 were observed.

Three children had a history of eczema and were observed to have eczema either on admission or during follow-up period (cases 2, 5, and 10). Two patients (cases 13 and 19) had severe seasonal hay fever. One had been receiving year-round desensitization injections for about a year at time of onset of nephrosis. The other patient received desensitization injections after the development of the nephrotic syndrome without benefit. This patient had several relapses during periods of exacerbation of hay fever symptoms. Several other patients (noted

above) had recurrent respiratory infections, or respiratory infections with a suggestive relationship to their renal disease. Another patient (case 23) had fever and rash with pertussis vaccine and a reaction to poison ivy during the year prior to onset of illness. This patient's brother has hay fever.

Renal biopsies were done in three adults. The diagnosis of primary amyloidosis was made in case 21 by means of renal biopsy; this was confirmed at postmortem examination. In cases 15 and 22, areas of thickened basement membrane with little or no cellular proliferation were seen in the glomeruli. In case 15 some glomeruli were completely replaced by hyaline masses. Response to steroid therapy was incomplete in case 22 and complete except for residual proteinuria in case 15.

Postmortem examinations were carried out here or elsewhere in all patients who died (cases 3, 8, 9, and 21). With the exception of the patient with amyloidosis, the kidneys in all cases had lesions which were considered to be those of "chronic glomerulonephritis." This term is unsatisfactory because to many clinicians it implies that the renal disease began as a typical attack of acute glomerulonephritis. We are using the term purely as the pathological descriptive term for the diffuse chronic glomerular lesions present. The kidneys were large rather than small and might be considered more characteristic of type 2 nephritis of Ellis [2] than of type 1.

Comment

As has been mentioned in the introduction, the present cases of the nephrotic syndrome have not been divided into diagnostic subgroupings except for the diagnoses of amyloidosis (case 21) and malarial nephrosis (case 1). What distinguishes the 3 patients with proteinuria without marked hypoalbuminemia and edema (cases 23, 24, and 25) from the first 22 patients with complete nephrotic syndrome may be only a matter of degree, but it seems to us that the development of the complete nephrotic syndrome might very well be dependent on more than simply the degree of proteinuria. The degree of proteinuria in these patients (cases 23, 24, and 25) was the same or greater than in patients of comparable body weight and age (cases 12, 17, and 14), yet only the latter three had marked hypoalbuminemia and increased serum cholesterol and edema.

In patients with comparable degrees of proteinuria, but without the complete nephrotic syndrome —patients often assumed to have chronic nephritis— steroid therapy in the few cases reported [9] did not produce any dramatic change. Three of the present patients (cases 23, 24, and 25) can be added to this experience. What relationship the slow improvement over two years noted in case 24 had to the steroid therapy is unclear. It is of interest that the patient with renal amyloidosis did not respond favorably to steroid therapy. This poor result in the nephrotic syndrome of amyloidosis is in accord with a similar observation by other observers.[10] It should be noted that symptomatic diuresis after steroid withdrawal did occur in the present case. The relationship of quartan malaria to the nephrotic syndrome has been reported previously and is discussed elsewhere.[5]

It is difficult to compare these results with steroid treatment of the nephrotic syndrome with those of other reports because of the small size of this group of patients, the differences in patients included, and the different methods of using steroid therapy. The originally employed 10-day course of steroid or adrenocorticotropin [11] in some cases produced real remissions associated with diminution or disappearance of proteinuria but in other cases produced the symptomatic type of steroid withdrawal diuresis shown by case 16 (fig. 6), not accompanied by a decrease in proteinuria or increase in serum proteins. These two types of response were often confused when effect on edema was considered without accompanying quantitative studies of urinary protein. Since at the end of 10 days of steroid administration marked changes in urine and serum proteins may still be occurring, it seemed reasonable to us to continue the initial course of therapy until there was no further decrease in proteinuria or increase in serum albumin; this required about one month in the present study. Prolonged initial courses of therapy were also employed by Greenman,[12] Merrill,[13] and Rapoport [14] and their co-workers, while Kramer and associates [15] followed an initial 10-to-17-day course of corticotropin with a second similar course, and Lange and associates [16] followed an initial 10-day course of adrenocorticotropin with intermittent high dosage of steroid. No evidence of beneficial effect was seen in the present study from a prolonged course of a dosage of prednisone below that which diminished proteinuria. It was not until the dose of steroid was raised to the level which decreased proteinuria (in most responsive cases 40 mg. of prednisone or 160 mg. hydrocortisone daily) that improvement occurred.

It is therefore our present policy in both adults and children to initiate therapy with 40 mg. of prednisone (or 160 mg. hydrocortisone) per day in four divided doses. The steroid administration is continued for at least 3 weeks, although no dramatic decrease in proteinuria was observed to begin later than the first 10 days of treatment. When a remission occurs, the dosage is continued until no further decrease in proteinuria or increase in serum albumin occurs. The dosage is then gradually reduced and discontinued. If proteinuria recurs, the therapy is reinstituted and continued until the occurrence of a second remission. In the present approach an attempt is made to adapt therapy to the needs of each individual patient, rather than to employ a rigid schedule of either short-term or long-term therapy.

Although Lange and co-workers [16] recommend placing on maintenance therapy all patients who have periods of remission as a result of initial corti-

cotropin or steroid treatment, we do not feel justified in arbitrarily committing all such patients to prolonged maintenance therapy, since only one patient (case 6, fig. 3) in our group has had repeated early relapses on discontinuing therapy. In this case there was no evidence that an amount of maintenance steroid less than the full initially effective dose prevented relapses, whether given daily or as double this daily dose for three successive days out of each six. We did not observe any decrease in side-effects of the steroids in this patient when they were administered in this interrupted fashion.

It is of interest that the disease in a patient such as case 16 (fig. 6), who remained unimproved, was clinically indistinguishable by the studies employed from that of case 20 (fig. 2) in whom a complete remission occurred. This difference in response to steroid therapy indicates that the renal lesion in the two cases differed, despite the failure of laboratory studies to distinguish the difference. It might be suggested that renal biopsy would help solve problems of this kind. However, an adult with moderate renal insufficiency (case 15) had a dramatic response to steroid therapy with marked improvement in renal function, although examination of renal biopsy showed marked interstitial inflammatory changes as well as periglomerular fibrosis and basement membrane thickening plus partial to complete hyalinization of at least half the glomeruli.

Certain tentative conclusions can be drawn from these studies about the prognostic significance of various features of the disease. Definite responses to steroid therapy occurred in children and adults—at least partial remissions occurred in approximately three-quarters of both groups. Thus the age of the patient in the present study has not been useful in predicting response to steroid treatment. At least as far as response to steroid therapy is concerned, the idiopathic nephrotic syndrome is fundamentally the same disease in children and adults. The urine of all of the present patients contained an abnormal number of red blood cells, therefore this finding appeared to be of little prognostic significance. Renal insufficiency of moderate degree was in many cases found to be at least partially reversible and not incompatible with a favorable response to steroid therapy.

Although the mechanism of the effect of prednisone and hydrocortisone on the nephrotic syndrome is unknown, it appears from this and other studies that the prime indication for steroid therapy in renal disease is the presence of the nephrotic syndrome. Steroid therapy is unquestionably beneficial for the short term in many patients with the idiopathic nephrotic syndrome. To what extent steroid therapy changes the long-term outlook remains to be seen, for it is generally thought that up to half the children might be expected to recover without it. In adults the prognosis is generally said to be poor,[17] although Addis [4] describes a group of adults with recurring nephrotic syndrome with benign prognosis, and Rosenheim and Spencer [18] have reported remissions in adults on conservative treatment plus ion-exchange resin. The high rate of remission in our group of adults suggests that steroid treatment is changing the outlook for these patients. This question may be settled by the results of long-range cooperative studies such as that conducted in children by Riley and co-workers.[19]

Summary

Of 20 patients with complete idiopathic nephrotic syndrome, 12 are well, 4 are improved, and 4 are unimproved or dead after steroid therapy. Steroid treatment was ineffective in one additional patient with nephrotic syndrome due to renal amyloidosis and in three patients with proteinuria but without the hypoalbuminemia and hyperlipoidemia seen in the classical nephrotic syndrome.

The therapeutic regimen found effective for the majority of patients was the daily administration of 40 mg. prednisone or 160 mg. hydrocortisone for as long as necessary to achieve the maximum clearing of proteinuria and increase in serum proteins, usually about one month, followed by gradual reduction of the dosage. In responsive patients a diminution in proteinuria was observed within the first 10 days of steroid therapy. In six patients who responded well but relapsed at various periods after discontinuing therapy, the initially effective regimen was repeated with success. Only one patient required maintenance therapy for recurrent relapses and in this case maintenance dosage below full therapeutic dosage was not successful. The simplest and most sensitive indication of a change in the disease was provided by frequent determination of the 24-hour urine protein. We have sharply distinguished between the diuresis accompanying a real remission and the "symptomatic" diuresis which may occur on discontinuing therapy in patients who have had no change in proteinuria or serum proteins.

In this series of patients the response to steroid therapy in adults did not differ greatly from that in children, and microscopic hematuria and moderate renal insufficiency did not necessarily preclude a good response. No essential difference in effectiveness or side-effects was noted between prednisone and hydrocortisone.

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RESEARCH IN STATE AND LOCAL HEALTH DEPARTMENTS

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Attempts have been made in the past to define public health research and to differentiate it from other areas of medical research. Although it has not offered a concise definition, a special committee, appointed nine years ago by the National Advisory Health Council of the United States Public Health Service, has provided a useful classification of public health research.[1] The five major categories suggested are as follows:

1. Studies related to the extent and distribution of diseases or other public health problems in a community, population, or part of a population.

2. Studies, on a community, population, or group basis, in relation to the pathogenesis or dissemination of diseases of public health importance.

3. Studies of the effectiveness of prophylactic or therapeutic procedures on a community, population, or group basis.

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As compared with other areas of medical research, the distinctive feature of public health research is that it is formulated on a community-wide basis or at least encompasses the study of readily definable population groups which can be subjected to observation and measurement. In cardiovascular disease, in arthritis and rheumatic disorders, in neoplastic diseases, in neurological and sensory disorders, in allergy, and in the problems of mental health, leading investigators and those who guide research programs are beginning to utilize epidemiologic techniques and to establish field studies. Careful critical inquiry directed toward the creation of new knowledge or the application of available knowledge to useful purposes offers the health officer, as well as his colleague in other branches of medical practice, a challenging opportunity.

4. Studies designed to test the significance of a laboratory or clinical finding, or to test the validity of a laboratory technique, on a community, population, or group basis in relation to problems of public health importance.
5. Studies in public health methods.

The last category is further subdivided into four groups:

(*a*) Studies designed to solve organizational and administrative problems faced by health agencies in the mass application of new methods of diagnosis, prevention, and control of diseases of public health importance, and in the application of new measures for the maintenance of health.
(*b*) Studies designed to test or develop epidemiological methodology, or other specialized methodology used or presumably useful in public health practice.
(*c*) Studies of the productivity of public health practices already in process.
(*d*) Studies of the applicability of theories and hypotheses in public health organization and administration.

The distinctive feature in each of the five categories enumerated above is that public health research is formulated on a community-wide basis or at least encompasses the study of readily definable population groups which can be subjected to observation and measurement.

Public Health Approach to Medical Research

It is increasingly realized that many of the major medical problems of the day, including the so-called chronic degenerative processes, may owe their origins as much to environmental stress and external precipitating factors as to intrinsic predispositions. More and more medical research is being directed to what well might be called the public health approach whereby the health problems of the individual, as well as the group, are studied in relationship to the total environment. In cardiovascular disease, in arthritis and rheumatic disorders, in neoplastic diseases, in neurological and sensory disorders, in allergy, and in the problems of mental health, leading investigators and those who guide research programs are beginning to utilize epidemiologic techniques and to establish field studies. There is hope of gaining thereby better understanding of the pathogenesis and of the basic mechanisms influencing the occurrence of the disease or diseases under study. From such efforts, too, there can be derived fruitful leads for further and more detailed investigation under the more readily "controlled" environment of the laboratory and clinic.

As a result of this growing interest in public health research, a limited number of health departments, on both state and local levels, are now being drawn into cooperative research undertakings with the more traditional centers of medical investigation. Well-organized health departments, with their time-honored utilization of epidemiologic methodologies and with "community-centered" orientation in their day-to-day activities, are valued collaborators in such studies. Some health departments, with qualified staff, have taken the initiative and established independent studies, often enlisting the assistance of university-based scientific personnel or others to supplement their own resources.

The official public health agencies of this country, on federal, state, and local levels, have placed high priority in the past on research as an integral part of their appointed tasks. The record of American public health work is replete with outstanding examples of fundamental studies and investigations leading to better understanding of the basic factors contributing to the occurrence, the distribution, the control, and the prevention of disease. The most readily documented research endeavors of scientists identified with public health activity have been in the area of the infectious diseases. Yet, productive research activity of physicians and other scientific personnel employed by official public health departments has not been, is not now, and will not in the future be restricted to communicable disease processes.

Status of Public Health Research at Community Level

As one surveys the national scene, it is apparent that the potential for fruitful research endeavor in state and local health departments is not being fully exploited. In the recently published report of the American Foundation,[2] entitled "Medical Research: A Midcentury Survey," the following statement may be found: "In most state and city health departments research is still the exception."

A recent analysis of research grants awarded by the Public Health Service offers confirmatory evidence. The research-grant program of the National Institutes of Health has grown since 1947 to sizable proportions and now constitutes the major source of support in this country of investigations in medical and related biological research. During this 11-year interval, research grants to investigators in state and local health departments have not kept pace with awards to their fellow workers in universities, hospitals, and similar institutions. In the six years from 1951 to 1956 the National Institutes of Health awarded a total of 15,342 grants in an aggregate amount of almost 162 million dollars. Only 96 of these grants, or about six-tenths of 1%, were made to state and local governmental agencies, including health departments. In dollar value, grants to state and local governments were less than 1% of the total. Moreover, taking the grants to health departments as a group, the number of grants made each year remained almost stationary (10 to 12 each year), whereas in the same six-year period all research grants made by the National Institutes of Health had more than doubled (from 1,684 to 3,439).

This small number of grants approved for state and local health departments is not the result of a low approval rate. Of all grant requests received by the division of research grants of the National Institutes of Health, the proportion of grant requests approved for health departments has been virtually

identical with that of grant requests from other sources. It can only be concluded that proposed projects are not being submitted in appreciable numbers by state and local health departments for support by Public Health Service funds. It is recognized that in a few large state or local health departments substantial research is supported by state or local tax funds. It is reported that one state health department uses one-eighth of its appropriation for the support of its research. This situation is exceptional.

In the light of available evidence it may reasonably be asserted that members of the public health profession are not now exerting a full measure of effort in seeking better understanding of the causes, diagnosis, treatment, and prevention of the major diseases and disabilities of man. Undoubtedly, there are multiple and varying reasons for the lack of substantial research programs in other than a few state and local health departments. There are three factors within health departments which we believe are of importance. These factors are as follows:

1. State and local health departments have been and are regarded as service organizations. The immediate urgency of service, particularly with insufficient staff for the work required, is an obstacle to the development of sustained research programs. In some states, legislative bodies by policy assign funds and the responsibility for research to state universities. This tendency to limit health departments to service functions has suppressed their interest in the development of research activity.

2. The favorable development of medical research in universities, medical schools, and hospitals is in part due to planning—planning of the research and for its support. Few health departments have taken any action designed to stimulate, guide, and assist in the development of an active research program.

3. For all activities in health departments and particularly for research, there is the problem of staffing. In a highly competitive area, health departments have had limited success in attracting workers qualified by training and experience for research. This unfavorable condition has been aggravated, since able young workers, who have been attracted to public health and who have retained their interest in research, have been drawn elsewhere by more favorable opportunities for research.

Steps Taken to Encourage Public Health Research

What steps have been, or are now being, taken to foster and encourage research activities in state and local health departments? Appropriate leadership has already been assumed nationally by both governmental and voluntary health agencies and by professional associations of health workers.

In 1950, under the chairmanship of Dr. Lowell J. Reed, there was a conference on methods in public health research, sponsored jointly by the public health study section of the National Institutes of Health and the graduate school of public health of the University of Pittsburgh.[3] The following year the Milbank Memorial Fund devoted its annual conference (1951) to the subject of research in public health.[4]

At its annual meeting in November, 1955, the Association of State and Territorial Health Officers [5] gave attention to research in public health and stated its official recommendations in the following resolution:

> That all state and territorial health departments accept research, taken in its broadest sense, as a fundamental part of public health work and that state and territorial health departments designate a person or committee within the department with the responsibility for operational research planning and program evaluation, and furthermore that adequate biostatistical services be developed in order to carry on this activity. That operational research conducted by health departments be directed primarily toward the following three areas: (*a*) research that can be expected to result in improved health, medical care, or rehabilitation services; (*b*) research that will determine the values of public health techniques and thus demonstrate the feasibility of eliminating outmoded procedures; and (*c*) research that will bring to bear on the chronic diseases the epidemiologic approach which health departments have applied successfully to the acute communicable diseases. That state and territorial health departments conduct operational research where possible in cooperation with universities.

At approximately the same time (November, 1955) the discussions provoked by the theme of the 83rd annual meeting of the American Public Health Association in Kansas City: "Where are we going in public health?" led to a series of conferences (December, 1955, and May, 1956) sponsored by the University of Michigan school of public health. According to unpublished reports, it was agreed that program evaluation, methodological studies, and operational research should warrant high priority in public health both at state and local levels. In view of current shortages of highly trained technical personnel and pressures to get jobs done, there has perhaps been a tendency to place less stress than, to some, seems warranted on fundamental or basic studies within organized public health departments.

More recently the so-called task-force conference, convened by the American Public Health Association at Arden House, Harriman, N. Y., in October, 1956, again reviewed many of the major problems confronting the public health workers of this country. The report of this conference and its recommendations have been approved in principle by the governing council of the association.[6] A new standing committee on research policy and a series of technical program committees "concerned with public health program areas," including their research implications, are already beginning to function.

Governmental Aid in Meeting State and Local Research Needs

Even more recently the Public Health Service has taken additional steps to strengthen public health research productivity, both in basic and applied investigations. As stated by Surgeon General Burney,[7] the Service "will do everything in its power

to promote and assist the development of research in, by, and with state and local health departments."

Within the last few weeks a newly enlarged and strengthened public health research study section has held its first meeting under the aegis of the division of research grants of the National Institutes of Health. In the membership of this study section there are included representatives of both state and local health departments, schools of public health, departments of preventive medicine in medical schools, voluntary health agencies, and other disciplines having bearing on public health research. These individuals have been asked not only to review and recommend to the appropriate national advisory councils and the surgeon general of the Public Health Service those grant applications warranting support on their scientific merit but also to advise as to how such research can best be fostered and encouraged.

In addition, a new advisory committee on epidemiology and biometry has been established at the National Institutes of Health and is seeking ways to strengthen and expand graduate training of individuals in these two important disciplines (at present epidemiologists and biometricians are in extremely short supply); the committee members will also serve as consultants to study sections and councils in the proper evaluation of grant applications involving these methodologies. It will be some time before the full effect of this program will be felt. Another Public Health Service training activity, the so-called title 1 public health traineeship program resulting from the act of 1956 amending title 1 of the Public Health Service Act, is already well under way, and individuals trained during its first year of operation are becoming available for assignment to a variety of public health tasks.

One institute of the National Institutes of Health has recently assigned a staff member to explore with state health departments—in this instance, directors of state public health laboratories—ways in which their research activities might be augmented. Moreover, a program designed to assure closer liaison between the National Institutes of Health and the state and local health departments through the Bureau of State Services of the Public Health Service is now evolving. Thus, high priority is being given to public health research by all segments of the Public Health Service.

In view of these encouraging developments, it may be asserted justifiably that at no time in the history of the public health movement in this country has the climate been more favorable for the establishment of vigorous and imaginative programs of research within organized public health departments. Accordingly, ways must be found to improve both the opportunities and the incentives in state and local health departments, so that strong, soundly conceived, and continuing research programs can be incorporated within the framework of their day-to-day activities. These opportunities must apply both to basic research—investigations which offer no immediate practical applications but may provide fundamental understanding of disease processes and thus, in the long run, contribute most to the control of disease—and to the more immediate types of operational studies and applied research.

Responsibility of Health Departments for Development of Research Programs

It is perhaps unnecessary to reiterate a well-established axiom of medicine (the science on which so many of the principles of public health practice are based) that research is essential to the establishment and maintenance of the highest standards of performance in all its assigned tasks. Few would quarrel with the view that the spirit of careful and critical search for new information must be an integral and continuing element in health department practice. We wonder, however, whether the risks involved in the absence of a research component in public health activity are as well recognized. These have been eloquently enumerated by Dr. Harry S. Mustard [8] in the following words:

> In the absence of a spirit and practice of inquiry, the health department is in danger on a number of counts. First, there is the danger that hypotheses or assumptions of the past, recognized as such when they were accepted, may gradually take on the stature of fact or reality. A second danger, in the absence of research or study, is a tendency in health departments to become confused as to what constitutes ends and what constitutes means of attaining these ends. This results in a situation where existing methods or practices are glorified and stoutly—even violently and vehemently—defended. The original ends to be attained have been lost to sight. A third hazard, where there is no inquiry and fresh knowledge, is that health departments, having established a given undertaking, may continue a full program of activities in this connection long after the particular problem has become relatively less important.

In the final analysis, responsibility for the development of productive research programs in state and local health departments rests with the departments themselves. A first requirement is that health departments accept research, in fact as well as in principle, as a proper and essential part of their activities. The evidence of this acceptance of research as part of the programs of health departments may be the establishment of an appropriate position, committee, or division to provide leadership in research. Secondly, it is basic to sound research that the investigators themselves have original ideas and sound plans for the study of some particular problem.

Thirdly, the initiation of research in health departments must involve the most effective utilization of resources already available to them. It should be remembered that research grants, no matter from what source they may be derived, are not designed to encourage individuals or groups to begin to give attention to research; their purpose is to provide aid to those who have made a sound beginning and have demonstrated productivity or promise in research.

Fourthly, if health departments are successfully to develop and strengthen their research programs, they must staff for research. The incorporation of a stimulating research program as a part of health department activities could be a major asset in attracting and retaining the able talent required and at the same time could elevate substantially the general quality of staff drawn into the field of public health.

Public Health Research as a Cooperative Enterprise

As has been pointed out recently, the volume of grant-in-aid support for medical and related research in this country has expanded rapidly in the last 15 years.[9] Increased governmental participation in this area has been particularly striking. These increases in government support have not reduced the contributions from philanthropy and other sources. Actually, private support for medical research has increased in the postwar period, although not in proportion to the expansion of federal aid.

As indicated, investigators in state and local health departments have not utilized these resources to the same degree as have their fellow researchers in hospitals, medical schools, universities, and other research centers. Dr. James A. Shannon,[10] director of the National Institutes of Health, offers encouragement to investigators in health departments in the following words:

> As the focus of modern medicine and the health sciences turns toward the chronic diseases, research workers must be prepared to tackle these problems simultaneously in the clinic, in the laboratory, and in the field. . . . The programs of the National Institutes of Health are broad enough to encompass research proposed by the staffs of state and local health agencies . . . there is no doubt but that the unique opportunities for research, particularly studies involving observation of man in his natural environment, by these agencies should be more fully exploited.

There are shortages of trained man power for research. To aid in overcoming this serious obstacle to productive research, research fellowships and traineeships have been made available through the Public Health Service to individuals seeking careers in scientific investigation. It may well be that some of the man-power shortages in public health research can be alleviated by further utilization of these resources.

Those concerned with research, in health departments as elsewhere, share the responsibility for mobilizing and utilizing advantageously the available research potential. Health departments, particularly at the local level, are experienced with activities which can be successfully executed only through the cooperation of practitioners. Many "community-centered" investigations will need the active participation of the physicians in the community. Local health departments are strategically situated to undertake studies of this type. State health departments should be ready also to aid in investigations with which practitioners, individually or as a group, are concerned, as, for example, through the provision of special laboratory or statistical services. With the development of research in state and local health departments, there will be increasing opportunities to cultivate the research resources now dormant among medical practitioners. This could be an unexpectedly valuable outcome of the development of research in our health departments.

Limited experience clearly establishes that the development of research in state and local health departments can proceed with unexpected rapidity. During the latter half of 1956 the Florida State Board of Health, on recommendation of the state health officer, formally accepted research as an essential part of its activity. A coordinator of research was designated, and a committee on research was appointed. The latter included staff members from the state and local health departments, representatives from the two medical schools in the state and from other interested university departments, and a practitioner who had displayed active interest in research. At its initial meeting the committee had the benefit of the advice of consultants from schools of public health and the Public Health Service.

Subsequently, it was recommended by the Florida Advisory Council on Training and Research in Mental Health that a conference devoted exclusively to research in mental health be arranged. This drew together those from mental hospitals and a variety of state agencies concerned with mental health; others who attended were from university departments of psychology, sociology, and social work, from the medical schools, and from the state and local health departments. The chairman of the committee on mental health of the Florida Medical Society was in attendance. Again, consultants from the National Institutes of Health and elsewhere aided richly.

These group discussions have been effective in developing and consolidating interest in broad cooperative research programs. Plans have evolved for the initiation of substantial research programs in two local health units supported by resources already available in the state. Other research programs are being developed gradually in a comparable manner. It has been gratifying to learn how much can be done without added support. Research interest and talent among younger health officers, previously unnoticed, are now apparent. The immediate and urgent need is for training opportunities in public health research. Although the beginnings are encouraging, it is recognized that accomplishments in research can be measured dependably only after the passage of 5 or 10 years or more.

Summary

The need for further development of research in public health is apparent. There are soundly established precedents for the integration of scientific investigation with the day-by-day service functions of both local and state public health agencies. If high standards of performance are to be maintained

and if the best-qualified personnel are to be recruited and held in public health programs, research becomes an indispensable component of health department responsibility. Many of the older problems confronting the public health officer still remain unsolved, and the complex newer problems, involving the chronic degenerative diseases and mental health, urgently demand research attention. Careful critical inquiry directed toward the creation of new knowledge or the application of available knowledge to useful purposes offers the health officer, as well as his colleague in other branches of medical practice, a challenging opportunity. The evolution of strong programs of research in public health departments could be the beginning of notable advances in public health.

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PREVENTION OF HEAT CASUALTIES

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and
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The incidence of heat casualties among recruits at a training center has been reduced appreciably since 1953 by limiting certain activities during periods of excessive heat. To avoid undue loss of time from programs of drill and physical conditioning, a closer adaptation of such activities to weather conditions was needed. An older index based on temperature and humidity alone was replaced by an index (WBGT) based on temperatures read with a shaded dry bulb thermometer, a shaded wet bulb thermometer, and a "globe" consisting of a thermometer enclosed within an unshaded, blackened 6-in. copper sphere. The closer adjustment of the training program to weather resulted in a further significant reduction of heat casualties in the summer of 1956, although it was hotter than the summer of 1955.

Since 1953 hot weather training policy at the Marine Corps Recruit Depot, Parris Island, S. C., has emphasized liberal water and salt intake by recruits, indoctrination of recruits and instructors in hot weather hygiene, rational clothing practices, and restriction of strenuous outdoor training for all recruits during periods of moderate to severe climatic heat. This preventive program proved effective in reversing the trend toward high rates of heat casualties noted in 1951 and 1952, but success was achieved only at considerable cost in hours scheduled for drill.

In 1956 the training command modified existing regulations in accordance with recommendations stemming from field studies supported in 1954 and 1955 by the Navy Bureau of Medicine and Surgery.[1] Two recommendations were (1) to test a new heat stress index based on weighted readings of instruments which measure thermal radiation and air

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movement, as well as air temperature and humidity; and (2) to establish two levels of climatic heat for suspending drill—a lower level for unseasoned recruits and a higher level to apply to all recruits alike. In addition to these modifications in hot weather regulations, the training program itself had undergone certain basic changes.

The incidence of heat casualties among recruits at Parris Island was significantly lower in 1956 than in 1955 despite higher seasonal heat in 1956. The purpose of this paper is to compare the incidence of heat casualties during these two summer periods in light of differences in the training program, hot weather regulations, and intensity of summer heat.

Training Program

Changes in the training program in 1956 as compared with 1955 are summarized in table 1. The two principal categories of training involving sustained energy expenditure at moderate-to-high levels are infantry drill and physical conditioning. Extending the training period from 10 weeks in 1955 to 12 weeks in 1956 reduced the number of hours of drill per week in 1956. However, this is more than offset by the increase in hours devoted to physical conditioning.

TABLE 1.—*Changes in Training Program Between 1955 and 1956, Marine Corps Recruit Depot, Parris Island, S. C.*

	1955	1956
Length	10 wk.	12 wk.
Local time	EST	EDT
Hr. drill (total)	97	109
Hr. physical conditioning (total)	17	48
Physical fitness test	No	Yes
Conditioning platoon	No	Yes
Obstacle course	No	Yes

Two categories of training involving high peaks of energy expenditure are bayonet drill and the obstacle course. The latter was introduced for the first time in 1956 as part of the physical conditioning program. It is significant for this study that both the bayonet drill and the obstacle course are deferred until the last three weeks of training.

Physical fitness is determined for each recruit early in training with the strength test described in chapter 17 of Army Field Manual 21-20. Conditioning platoons were established in 1956 for obese recruits and other recruits below standard in the physical fitness test. Periodic reexamination of recruits in the conditioning platoon determines when they are fit to return to regular training.

Hot Weather Training Regulations

Table 2 is a summary of the chief differences in the 1956 regulations as compared with 1955. In both years display of the yellow flag or red flag at two strategic areas on the depot compound was used to betoken prevalence of moderate or severe climatic heat. In 1955 the index was based on temperature and humidity only. The yellow flag was displayed at the edge of the drill field and near the rifle range when the air temperature was 90 to 100 F. This resulted in curtailing active outdoor drill for all recruits. The red flag was flown when air temperatures exceeded 100 F or when temperatures of 90 to 100 F were associated with humidities exceeding levels specified in the depot training order.[1a] The red flag required suspension of all active training and all outdoor instruction which could not be conducted with men standing or sitting in the shade.

TABLE 2.—*Changes in Hot Weather Regulation Between 1955 and 1956, Marine Corps Recruit Depot, Parris Island, S. C.*

	1955	1956
Heat stress index	Air temperature and humidity	WBGT index sum of: 0.7 Wet bulb 0.1 Dry bulb 0.2 Globe temp.
Yellow flag (modified training)	90—100F dry bulb and low humidity	85—87.9F
Red flag (suspended training)	90—100F dry bulb and high humidity or dry bulb over 100	88F and over
Recruits affected	Yellow and red flags apply to all recruits	Yellow flag applies only to recruits in weeks 1, 2, 3, and 8
Acclimatization policy (first week)	None specified	Drill limited to 1½ hrs/day 5-min. break after 30-min. drill Physical conditioning limited to 15 min./day

As a substitute for the temperature-humidity index, two indexes were considered: the heat stress index (HSI) of Belding and Hatch,[2] and the wet bulb–globe temperature (WBGT) index of Yaglou.[3] Both had been tried in the field, and in addition good agreement was found to exist when these two formulations were applied to the same set of climatic data. The WBGT index was recommended to the training command because of greater ease in handling by enlisted personnel lacking special technical knowledge.

The WBGT index is based on readings of three instruments: 1. The shade dry bulb thermometer is an ordinary thermometer which reads air temperature. 2. The wet bulb thermometer is an ordinary thermometer with a moist wick surrounding the bulb. The wet bulb reading is the same as the corresponding dry bulb only when the atmosphere is saturated with water vapor (100% relative humidity). As relative humidity decreases, an increasing depression of the wet bulb below the dry bulb reading occurs as a result of evaporative cooling of the wet bulb. As used at Parris Island the wet bulb is shaded and cooled by natural convection. 3. The globe thermometer is a hollow copper ball 6 in. in diameter painted matte black on the outside and provided with an ordinary thermometer inserted through an airtight stopper with the stem exposed for reading. The black surface absorbs incident radiation from the sun and also from surfaces in the environment which exceed the globe surface in temperature. It loses heat to the cooler air by convection and to cooler surfaces by radiation. In an

unshaded outdoor position the globe reading is normally above the dry bulb reading. Daytime readings 20 F or more above air temperature are observed under calm clear conditions. Either a decrease in radiant heat load such as occurs when clouds obscure the sun, or an increase in wind velocity, or both, will lower the globe reading. Since the reading is a balance between heat gained by radiation and heat lost by convection, the globe in effect integrates radiation, air movement, and air temperature. Thus the combination of globe temperature and wet bulb temperature takes into account all four physical variables of the thermal environment.

Because of the simplicity of the instruments, any person capable of reading an ordinary thermometer can take the three readings. The WBGT index is calculated using the following formula, which requires the weighting of the three temperature readings as follows: 0.2 black globe temperature + 0.1 dry bulb temperature + 0.7 wet bulb temperature. Yaglou has found that this formula yields a figure differing only slightly from the effective temperature including radiation and has the advantage that it is more simply derived.[4] The formula for WBGT is stated by Yaglou to take into consideration the reflection of solar radiation by the khaki colored cotton fabric worn by recruits in military training. At Parris Island the derivation of the WBGT index differs from that specified by Yaglou in that the shaded wet bulb rather than the natural wet bulb is employed. The latter differs from the former in being exposed to sun as well as wind.

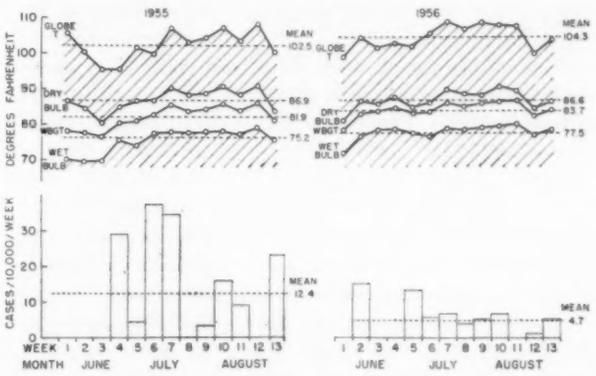
Under the 1956 regulations the yellow flag is flown at WBGT levels in the range of 85 to 87.9 F. Under these conditions active outdoor training is suspended for recruits in the forming period, during the first three weeks of training, and in the eighth week which follows three weeks on the rifle range and one week of mess duty. At WBGT levels of 88 and upward the red flag is flown, requiring the suspension of active outdoor training for all trainees with the exception of those on the M-1 rifle range during the fifth and sixth weeks of training. This sole exception to the red flag regulations was permitted by the training command as a necessary expedient in fulfilling training schedule demands.

Breaking-in of new recruits, first established as a prescribed policy in 1956, is accomplished by graduated intensity of physical conditioning exercises during the first week and thereafter, and by limiting infantry drill to one and one-quarter hours per day for the first week with 5-minute breaks after each 30 minutes of drill. After the first week as many as four hours of drill per day is permitted.

Minor differences in hot weather regulations for the two years include the use of aluminum-painted helmet liners in 1956 instead of the olive drab colored liners used in 1955 and, in 1956, recruits were required to carry only one full canteen of water into the field instead of two as called for by 1955 regulations.

Weather

Weather conditions were recorded hourly from 0800 until 1700 at an instrument station situated near the edge of the drill field and at another station near the rifle range. The data to be presented here are those recorded near the drill field. The wet bulb and dry bulb thermometers were located within a standard ventilated instrument shelter four feet above ground level. The 6-in. black globe thermometer was supported at the same height in an unshaded position nearby. Each instrument was read on the hour from 0800 through 1600 local time in 1955 and through 1700 local time in 1956. Saturday readings included those through 1200 only. Readings on Saturday afternoons, Sundays, and holidays are not included in this report since these are not considered working days. Local time was Eastern Standard Time in 1955 and Eastern Daylight Time in 1956. Subsequent comparisons of weather data will be based on local time unless otherwise stated.



Mean weekly temperatures during working hours from 1000 to 1600 weekdays and 1000 to 1200 Saturdays, and mean weekly incidence of heat cases among recruits, Marine Corps Recruit Depot, Parris Island, S. C., June 1 to Aug. 31, 1955 and 1956.

The upper graph in the figure gives the mean weekly dry bulb, wet bulb, and globe thermometer temperatures together with the mean weekly and mean seasonal WBGT indexes for the 13-week period beginning June 1 and ending Aug. 31 for 1955 and 1956. The difference in the mean seasonal WBGT based on hourly readings for 1955 and 1956 has been analyzed statistically and found to be significant ($p<0.001$). Thus it appears that the summer of 1956 was hotter than the summer of 1955.

In comparing the number of hours in the heat stress zone on the basis of local time, we find that there were 112 hours of 85 to 87.9 F (WBGT index) and 15 hours of 88 F and above in 1955. In 1956 on the same basis of local time there were 140 hours

of 85 to 87.9 and 43 hours of 88 and above. Thus there were 44% more hours in the heat stress zone during corresponding hours of training in 1956 as compared with 1955.

If one assumes that there was active outdoor training scheduled for each of these hours, it is of interest to compare the maximum number of daytime training hours potentially lost per man in the summer of each year. In 1955, since both levels of heat stress apply to all trainees, each recruit potentially lost 127 hours (112 + 15) of training. In 1956, on the other hand, only about one-third of the recruit population stopped active outdoor training during the 140 hours in which the WBGT level was 85 to 87.9. Therefore, in 1956, potential loss of training per man was 89 hours (⅓ × 140 + 43). Thus there were 44% more hours in the heat stress zone in 1956, but the potential loss of training was actually 30% less than in 1955.

Incidence

In this report a heat casualty is considered to be any trainee admitted to the depot dispensary where examination by a medical officer establishes a diagnosis of heat exhaustion, heat stroke, or heat cramps. Special report forms were filled out following clinical examination by the medical officer and submitted to the Navy Bureau of Medicine and Surgery.

In the 13-week period from June 1 to Aug. 31, 41 cases of heat exhaustion and one case of heat stroke were reported in 1955, and 41 cases of heat exhaustion and four cases of heat stroke in 1956. No cases of heat cramps were reported either year. The mean weekly recruit strength in 1955 was 2,589 as compared with 7,407 in 1956. Thus, the mean weekly incidence rate of heat casualties was 12.4 per 10,000 in 1955 and 4.67 per 10,000 in 1956. This difference has been analyzed statistically and is found to be significant ($p<0.001$).

The lower graph in the figure gives the weekly incidence rate per 10,000 trainees for each of the 13 weeks from June 1 to Aug. 31 of each year in relation to indexes of climatic heat for each week plotted on the upper graph. Peaks of incidence of heat cases are less well defined in 1956 than in 1955. This may be because the heat is more sustained than in 1955 or it may be because the new regulations and training procedures in 1956 succeeded in preventing or blunting the point of outbreaks of heat illness.

The type of activity being undertaken by the recruit at the time he became a casualty was reported in each case. In both years, infantry drill accounted for slightly more than 50% of the total number of cases. Physical conditioning was relatively more important as a predisposing factor in 1956 than in 1955, as might be expected in view of the greater number of hours devoted to this activity in the 1956 training schedule.

The proportion of total cases occurring in the forming period and during successive weeks of training is shown in table 3. In both years the greatest proportion of cases occurred in the forming period and the first week of training. In 1956 this early period accounts for over 50% of all cases. On the other hand a relatively small proportion of total cases occurred after the fifth week in 1956 even though there are seven weeks included in this late period as compared with five weeks in 1955. The difference is significant at about the 5% level ($0.05 < p < 0.10$). This would seem to indicate that trainees in later weeks of training in 1956 represented a group more resistant to heat effects than in the preceding year.

The mean daily WBGT level for the hours from 1000 to 1600 of each week day and 1000 to 1200 on Saturday has been calculated for the period of June 1 to Aug. 31 of 1955 and 1956. With the exception of one day in 1955, no cases were reported for either year when the mean daily WBGT level was below 81 F, which thus represents the threshold level for heat casualties. In 1955, there were 50 days in the reporting period with mean daily WBGT levels of

TABLE 3.—*Proportion of Heat Casualties Occurring in Marine Corps Recruits During Forming Period and Subsequent Weeks of Training, Parris Island, S. C., June 1 to Aug. 31, 1955 and 1956*

			Wk. of Training					
	Cases	Forming Period	1	2	3	4	5 and Over	Total
1955	No.	5	8	9	4	0	16	42
	%	11.9	19.1	21.4	9.5	...	38.1	100
1956	No.	15	10	7	7	0	6	45
	%	33.3	22.2	15.6	15.6	...	13.3	100

81 F, or above. In 1956, there were 67 days in this category. Aside from an initial rise in the incidence rate per day at daily WBGT levels of 81 and 82, a continuing positive correlation between higher levels of the mean daily WBGT level and incidence rate per day is not seen. This can be attributed to the existence of the preventive program. Earlier reports [4] show that in the absence of regulations which curtail training during higher levels of heat stress, the incidence rate continues to follow an upward course.

Comment

As is true in any disease, heat illness is caused by the interaction of multiple factors, climatic heat being only one of these. Other factors of primary importance are the rate and duration of metabolic heat production during work, the interference of clothing with the dissipation of body heat, lack of acclimatization to heat, and deficiency of body water and salt. Secondary factors include lack of physical fitness, malnutrition or overnutrition associated with obesity, inadequate periods of recovery between bouts of work, fatigue from insufficient

sleep, postprandial heat exposure, and the existence of intercurrent illness such as febrile reactions to immunizing inoculations and skin eruptions.

The influx of unseasoned and physically unconditioned recruits and reserve trainees into military training centers maintains a group susceptible to heat stress. A recent survey of the incidence of heat diseases among Navy and Marine Corps personnel from 1951 to 1955 [5] reveals a higher incidence of heat casualties among trainees than among nontrainees stationed in the same geographical area.

A preventive program introduced at Parris Island and effectively enforced since 1953, has appreciably reduced the impact of environmental and individual factors which lead to excessive heat strain and heat illness in susceptible subjects. An important aspect of this program was the curtailment or suspension of drill during periods of excessive climatic heat. This serves to reduce heat loads resulting from environmental exposure as well as from metabolic heat production. The drop in incidence from a peak of 53 per 10,000 trainees per week in the summer of 1953 to less than 10 in 1954 testifies to the success of the control measures. To achieve this end, however, it was necessary to sacrifice time scheduled for drill and other strenuous activities. In 1956 regulations were modified by introducing a new index which was intended to provide a more valid appraisal of climatic heat by integrating all four thermal factors, including radiation and air movement as well as air temperature and humidity. Also the unseasoned recruit in his first weeks of training was recognized as being in need of greater protection than the recruit later in training; hence, training restrictions at lower levels of heat stress were changed to apply only to the new recruit.

Had these been the only modifications in hot weather training policy between the two years of 1955 and 1956, evaluation of the effectiveness of the new index would have been considerably simplified. In point of fact, important changes were introduced into the training program itself. Those which have direct bearing on the problem of heat and its effects on trainees relate to first, the length of training, which was extended from 10 weeks in 1955 to 12 weeks in 1956; second, the introduction of an intensive physical training and conditioning program; third, the isolation of obese and other physically substandard recruits in special training platoons; and finally the establishment of the breaking-in period during the first week of training. Even the change from standard time in 1955 to daylight time in 1956 played a role in reducing heat stress by shifting training hours toward the cooler portion of the day.

However difficult it may be to evaluate the part played by individual factors which were altered between 1955 and 1956, nevertheless certain important changes were observed in the incidence of cases, and the proportion of cases occurring in successive weeks of training. The over-all incidence of cases in 1956 was less than half that in the preceding year in spite of the significantly higher levels of climatic heat in 1956. Moreover, in 1956 the lower levels of heat stress (WBGT 85 to 87.9) constituting over 75% of the total hours of restricted training applied to only one third of the recruit population, namely, those in the forming period, the first three weeks, and in the eighth week of training. The more seasoned trainees, making up the remaining two-thirds of the recruit population, continued to train until the level of heat stress reached 88 or above. One might have anticipated that the older recruit deprived of the protection of the yellow flag would become a heat casualty at least as often as his counterpart in the previous year. This was not the case. In 1956 the proportion of cases that occurred in the fifth week of training and thereafter was appreciably smaller than in the previous year. Therefore, in 1956 it would appear that the older trainee had acquired higher tolerance to heat effects and that the principal source of improvement in the incidence in 1956 was a reduction in the occurrence of heat casualties in this more seasoned group. Whether this is primarily due to improved physical conditioning or to the acquisition of a higher level of physiological acclimatization to heat cannot be decided on the basis of the available evidence.

Related to the reduced incidence of heat casualties among trainees in later weeks of training, we observe in 1956 a greater proportion of cases occurring in the forming period and the first week of training. Fifty-five per cent of all cases reported in 1956 occurred in this early period compared with 31% during the same period in 1955. It is also noted that one-third of all cases in 1956 occurred before training actually began, that is, during the period the platoon was being formed. It is difficult to say whether the shift in the proportion of cases toward the earlier weeks of training is real or merely a manifestation of the reduced incidence among recruits later in training.

There was one case of heat stroke in 1955 and four in 1956. No fatal cases of heat stroke have been reported since 1953. All five of these cases of heat stroke occurred within the first two weeks of training. The greater number occurring in 1956, therefore, cannot be ascribed to the change in flag policy. Four of the five cases of heat stroke occurring in this two-year period were in obese recruits.

Earlier reports of heat stress studies at Parris Island and other Marine Corps training bases [1] emphasize the deficiencies of the heat index based on temperature and humidity alone. It is not possible to apply statistical analysis to the incidence of cases in relation to conditions of climatic heat or to any over-all index of heat stress. One reason for this is that the numbers of cases are limited. Secondly

the regulations themselves make such a correlation impossible. However, it is reasonable to believe that the WBGT index which is based on all physical factors of the thermal environment provides a more reliable criterion of climatic heat stress than the former index which was based only on temperature and humidity. To this extent the training program benefits by losing fewer hours of training under conditions which are not potentially hazardous to trainees. The trainee, on the other hand, benefits by not being required to train under conditions of intense solar heat loads and low wind velocities. These conditions are better interpreted as representing heat stress by the WBGT index than by the older index based on temperature and humidity alone.

Summary

Between 1955 and 1956 modifications in the recruit training program and hot weather training regulations were adopted by the training command at the Marine Corps Recruit Depot, Parris Island, S. C. Changes in the training program included a longer period of training and more hours devoted to physical conditioning. Special conditioning platoons were established for obese recruits.

Changes in the hot weather training regulations included the adoption of a heat stress index based on weighted reading of dry bulb, wet bulb, and globe thermometers (wet bulb–globe temperature index of Yaglou) in place of the former index which was based on readings of the wet bulb and dry bulb alone. In 1955 regulations, lower levels of heat stress resulted in restriction of strenuous training for all recruits but in 1956 only recruits in early weeks of training and in the eighth week after a week on mess duty were affected. Under severe climatic heat loads, training was restricted for all recruits in both years.

Based on the number of hours during the training day with WBGT levels of 85 or above, the summer of 1956 was significantly hotter than 1955. The mean incidence of heat casualties in the summer of 1955 was 12.4 per 10,000 trainees per week as compared with 4.67 per 10,000 trainees per week in 1956. This difference is statistically significant ($p < 0.001$). A relatively large proportion of the cases in 1956 occurred during the forming period, and in the first two weeks of training.

Because the lower levels of heat stress applied to only about one-third of the recruit population in 1956, the potential number of hours of drill lost per recruit because of heat was 30% less than in 1955 in spite of there being 44% more hours in the heat stress zone in 1956. The 1956 recruit in later weeks of training appears to have been more tolerant to heat effects than his counterpart in 1955. Physical conditioning combined with graduated exposure to higher levels of heat allowed by the 1956 regulations may have resulted in improved physiological acclimatization to heat.

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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Sex Chromatin in Forensic Medicine.—The existence of a sex difference in the morphology of intermitotic nuclei may be of importance, not only anatomically and clinically, but also for its value as an additional method of sex determination in forensic medicine. We have already shown that the presence of sex chromatin in the female nucleus can be utilized to determine the sex of unfixed human tissues which have been immersed in water or exposed to atmospheres of varying humidity and temperature. This nuclear feature persists for a period of 2-3 weeks, depending on the nature of the environment in which the tissues decompose. Further investigations . . . on the persistence of sex chromatin after death have since been made and emphasize the importance of our previous findings. Portions of full-term human female fetal tissue were buried in direct contact with the soil, some two feet from the surface. At regular intervals small fragments of skin, muscle and cartilage were removed, prepared by routine histological techniques and the nuclei examined for the presence of sex chromatin. The sex of the tissue could be determined in this way with certainty for four weeks after burial, which was considerably longer than had been the case with tissues degenerating in other environments.—A. D. Dixon, and J. B. D. Torr, Sex Chromatin as an Aid to the Identification of Sex in Forensic Medicine, *Nature*, Oct. 13, 1956.

CLINICAL NOTES

A SIMPLE TECHNIQUE FOR BRONCHOGRAPHY

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The need for a simple reliable technique for bronchography has been accented by the increased range and utility of this diagnostic procedure. The advent of readily eliminated contrast mediums and safer topical anesthetics are responsible for this change, and bronchography is now used as a diagnostic tool for many parenchymal, as well as bronchial, disorders of the lung. It should be stated that none of the individual features of the technique to be described are original, and that its present status was achieved by trial and error from methods developed by others.[1]

Premedication for bronchography is accomplished with pentobarbital (Nembutal): 0.1 Gm. for a stoical or composed person and 0.15 to 0.2 Gm. for an anxious or corpulent patient. This is given orally one hour prior to bronchography. Atropine sulfate (0.4 mg. for a person weighing 88 to 132 lb. [40 to 60 kg.] and 0.6 mg. for one of greater weight) is given subcutaneously one-half hour prior to the procedure. The advantage of having a dry mucous membrane to accept the local anesthesia far outweighs the possibility of inspissating secretions in the bronchial tree. No other preparation is necessary unless the patient has a productive cough in which event he is instructed to use postural drainage for 5 to 10 minutes immediately prior to the procedure.

The patient is then taken to the fluoroscopy room and asked to sit on the table with his legs over the side. An emergency tray (fig. 1) containing 30 cc. of a 2.5% thiopental (Pentothal) solution, a laryngoscope, an endotracheal catheter with stylet, and a machine to deliver oxygen by mask or through the endotracheal tube are present in the room during the entire operation. A history of allergy or reaction to local anesthetics and iodine is again elicited from the patient (having been done previously on the admission history). If positive, skin testing is performed; if not, the anesthesia is initiated. The patient is then asked to extend his tongue over his chin, grasping it with a 4-by-4-in. gauze dressing. The pharynx is then sprayed thoroughly two times with a flexible tip atomizer using 5% hexylcaine (Cyclaine) hydrochloride.[2] The patient is requested to breathe in and out rapidly during this action and not to swallow any of the anesthetic. Next, the nasal passageway with the better airway is sprayed two times while the patient inhales slowly and deeply. A 16 F. radiopaque urethral catheter is then inserted through the anesthetized nasal passageway while the patient again extends his tongue and inhales deeply or coughs (fig. 2).

With a little practice one can intubate the trachea almost every time. In fact, in my last 85 bronchograms I have been successful every time. With the tube in the trachea the patient will usually strain

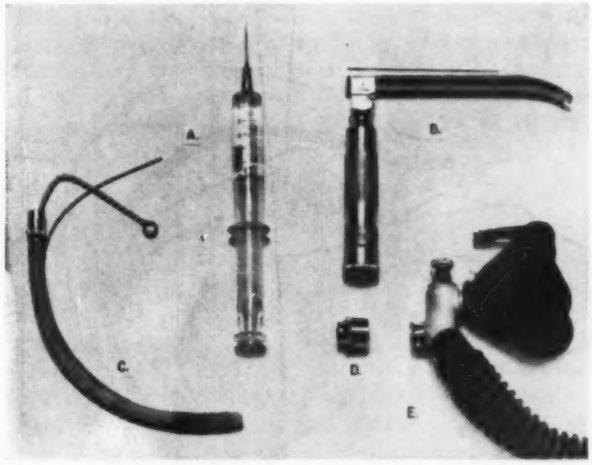

Fig. 1.—Emergency tray: *A*, 30 cc. syringe filled with 2.5% thiopental solution. *B*, laryngoscope. *C*, endotracheal tube with stylet. *D*, universal adapter. *E*, oxygen mask with tubing connected to an anesthesia machine or resuscitator.

for several seconds; however, a syringe containing 6 cc. of 5% hexylcaine is quickly attached and 3 cc. injected slowly during inhalation. This is repeated in two or three minutes, injecting the remaining 3 cc. In about five minutes the patient is placed on his side with his neck flexed laterally toward the ceiling and the catheter turned and advanced into the dependent main-stem bronchus. The patient is then turned onto his back and the position of the catheter determined by fluoroscopy. A syringe containing 40 cc. of propyliodone (Dionosil Oily) is attached to the catheter and handed to the assistant, who stands at the head of the table and injects the

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oil as the fluoroscopist proceeds. The lower lobe is filled first while the patient is on his back and the foot of the table is lowered. (It is usually necessary to have the patient take several deep breaths to facilitate filling the distal bronchi in all lobes.) Subsequently, the upper lobe is mapped with the patient lying on his side while the head of the table is lowered and raised several times. The anterior segment of the upper lobe is filled while the head of the table is down and the patient is in a semiprone position. The middle lobe is filled last, with the patient prone and the foot of the table down. The table is then leveled and the lung carefully inspected to make sure all segments have been mapped. Thus, with the use of the fluoroscopic table, one can visualize the filling of all segments of the lung with one complete rotation of the patient. He is then quickly placed in front of the cassette holder and posteroanterior and lateral projections of the chest are taken (fig. 3). If both sides are filled, posteroanterior and both oblique projections are taken.

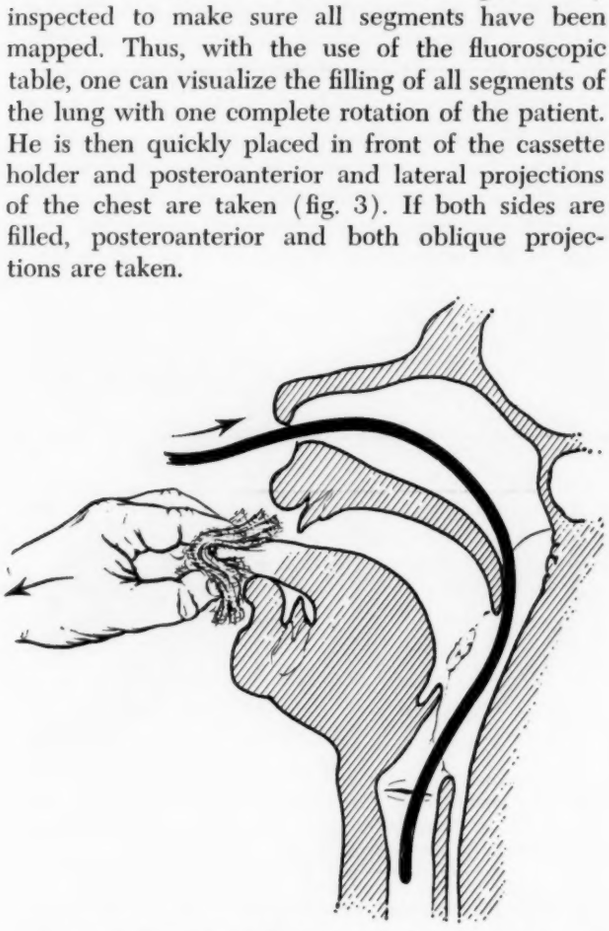

Fig. 2.—Transnasal intubation of trachea. Tongue is extended and catheter advanced into trachea while patient inhales or coughs.

If mapping of both sides is necessary it is better to do this in two sittings; however, for economy and expediency it is often necessary to do both sides at once. Stereoscopic films in the posteroanterior projections are helpful if both lungs are mapped, because of the excellent three-dimensional effect.

In the last 100 bronchographic procedures 82 of the bronchograms were excellent, 10 were satisfactory, and 8 were unsatisfactory. The chief causes of failure in this series were unsatisfactory premedication and the attempt to combine bronchoscopy and bronchography. The patient who has profuse secretions rarely obtains a good surface anesthesia, and if he is apprehensive it is difficult for him to cooperate. The majority of our patients who have combined bronchoscopy and bronchography do well, although there is a sizable minority who do poorly because of fatigue or loss of surface anesthesia. It is far better to delay bronchography, if the patient is not prepared physically or emotionally, than to have it result in a shoddy procedure.

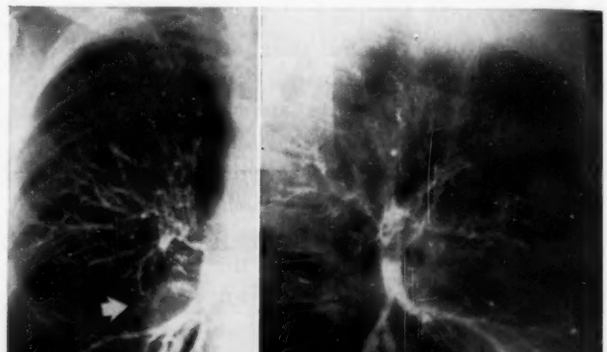

Fig. 3.—Posteroanterior and right lateral bronchograms showing obstruction and ectatic changes of right lower lobe segmental bronchi caused by bronchogenic carcinoma.

Summary

A simple reliable technique for bronchography uses a minimum of equipment with a maximum of efficiency. This method has yielded satisfactory bronchograms in 92 of the last 100 procedures.

4500 S. Lancaster Rd. (2).

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USE OF A NEW CORTICOSTEROID (ARISTOCORT DIACETATE) IN DERMATOLOGY

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Since the introduction of the corticosteroids, there has been a continuing search for newer compounds which would have equal or greater therapeutic efficacy and which would produce fewer adverse reactions in patients on prolonged maintenance therapy. The Δ^1 analogues of cortisone and hydrocortisone (prednisone and prednisolone) have been the most active of the available corticosteroids. Moreover, with these drugs, the incidence of sodium retention, excessive potassium depletion, and hypertension has been considerably reduced.

The purpose of this clinical study was to evaluate the anti-inflammatory and antipruritic properties of a new steroid compound, Aristocort diacetate (also known as triamcinolone diacetate), in a variety of severe dermatological disorders. The formula of this new steroid is Δ^1 9α-fluoro-16α-hydroxy-hydrocortisone-diacetate, and it was synthetized by Bernstein and others.[1] Animal assays indicate that this compound will not produce sodium retention and that it is 18 to 36 times more potent than hydrocortisone in the rat liver glycogen test. A report by Hellman and others,[2] dealing with its metabolic activity and use in rheumatoid arthritis, showed that the drug produced a profound antirheumatic effect, and metabolic studies showed that there was little change in nitrogen, calcium, or potassium balance with the use of this steroid. Patients showed a significant loss of sodium and water during these balance studies, and those who previously had been on steroid therapy had a significant weight loss. Sherwood and Cooke,[3] reporting on its use in bronchial asthma and allergic rhinitis, found that Aristocort was approximately twice as potent as prednisone or prednisolone on a weight basis and that there were no significant side-effects. The purpose of this preliminary study was to determine the therapeutic efficacy of Aristocort and the incidence and severity of side-effects as compared to that observed with the Δ^1 analogues of cortisone and hydrocortisone.

Method of Study

Twenty-six patients were selected from private practice, 15 males and 11 females. Their ages ranged from 8 to 66 years. They presented severe dermatoses, often generalized, with marked inflammatory changes and uncontrollable pruritus. Most of them had previously received prolonged courses of prednisolone therapy with satisfactory results, although many had developed side-effects such as moon facies, buffalo hump, increased appetite, weight increase, and gastrointestinal disturbances. Two had never been treated with orally given corticosteroids.

In those patients who previously had been on prednisolone therapy, treatment with the new compound was initiated only after they developed a severe relapse on maintenance doses. On each visit, weight and blood pressure were determined and urinalysis was performed. No dietary limitations, such as sodium restriction, were imposed, and no supplemental potassium was prescribed.

Aristocort was administered in four doses daily. In some persons, the initial suppressive dosage was identical with the previous maintenance level of prednisolone, ranging from 10 to 20 mg. per day. The maximum initial dosage was 32 mg. Maintenance levels of Aristocort required for complete control of symptoms varied from 4 mg. up to 16 mg. daily.

Observations

Patients were observed at weekly intervals, and the period of observation in the study ranged from 4 to 14 weeks. Because of the short period of observation, it is not possible to make any definite statistical evaluation, but some general observations were obtained. Aristocort has strong anti-inflammatory and antipruritic properties. It was also noted that the initial clinical response was as rapid as that obtained with prednisolone. In most patients, marked improvement was obtained within three to four days after institution of suppressive doses, and an average of eight days was required for complete control of symptoms and disease activity. The maintenance dosage was determined by clinical follow-up of each patient.

Sixteen patients with generalized incapacitating atopic dermatitis showed marked improvement, with decrease in erythema and relief of pruritus. The condition of some was still completely controlled on a minimal dosage of 4 to 6 mg. daily. Similar results were obtained in two patients with dermatitis herpetiformis. In two patients with exfoliative dermatitis of long duration, who had relapsed while receiving 20 mg. of prednisolone daily, the condition was adequately controlled with 20 mg. of Aristocort and then maintained satisfactorily on 10 and 12 mg. daily respectively. The condition of a third patient with exfoliative dermatitis, who re-

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lapsed while receiving 15 mg. of prednisolone, was controlled with 12 mg. of Aristocort daily. The condition of one patient with severe generalized angioneurotic edema was completely under control 48 hours after initiation of therapy with 32 mg. of Aristocort daily. A patient with alopecia totalis showed considerable regrowth of hair two weeks after initiation of therapy with 32 mg. of Aristocort daily. This patient had shown a similar response to the Δ^1 analogues, but not until four weeks after initiation of therapy with 40 mg. daily (table 1).

TABLE 1.—*Dosage of Prednisolone and of Aristocort Diacetate Given Twenty-six Dermatological Patients*

Case No.	Age, Yr.	Sex	Diagnosis	Duration of Disease, Yr.	Prednisolone, Mg.		Aristocort Diacetate, Mg.		Duration of Treatment with Aristocort, Wk.
					Initial Dose	Maintenance	Initial Dose	Maintenance	
1	31	M	Atopic dermatitis	20	60	30	30	16	6
2	64	M	Exfoliative dermatitis	6	40	20	20	8	16
3	57	M	Exfoliative dermatitis with arthritis	30	60	20	20	8	12
4	15	M	Atopic dermatitis	7	40	20	20	16	4
5	16	F	Atopic dermatitis	14	40	10	16	4	12
6	66	M	Infectious eczematoid dermatitis	2	40	20	20	16	13
7	51	M	Atopic dermatitis	30	40	20	20	16	10
8	56	M	Contact dermatitis	1	60	20	20	4	13
9	36	M	Atopic dermatitis	28	40	15	12	4	16
10	35	F	Atopic dermatitis	32	40	10	12	4	17
11	8	M	Atopic dermatitis	7	20	15	10	6	4
12	46	M	Atopic dermatitis	6	40	15	12	8	4
13	24	F	Atopic dermatitis	9	40	10	32	16	4
14	30	F	Angioneurotic edema	1 mo.	...	...	32	...	4
15	26	F	Atopic dermatitis	3 mo.	...	...	32	...	4
16	47	F	Alopecia totalis	1	40	40	32	24	4
17	59	M	Pemphigus erythematosus	2 mo.	60	15	12	8	6
18	16	F	Atopic dermatitis	11	40	15	20	12	4
19	27	F	Atopic dermatitis	16	30	15	16	10	7
20	29	F	Atopic dermatitis	11	30	15	16	10	7
21	41	F	Atopic dermatitis	40	50	20	12	12	4
22	42	M	Dermatitis herpetiformis	7	50	20	24	12	15
23	23	M	Dermatitis herpetiformis	1	60	20	20	16	3
24	33	M	Atopic dermatitis	Entire life	30	25	28	16	11
25	45	M	Exfoliative dermatitis	4	40	15	12	8	8
26	53	F	Atopic dermatitis	1	40	15	12	10	4

We also attempted to determine the equivalent dosage of Aristocort as compared to prednisolone. In each patient, the therapeutic response during both courses of therapy was carefully evaluated. The results are reported in table 2. It was noted that Aristocort was more active than prednisolone, in that similar therapeutic efficacy was obtained with two-thirds to three-fourths of the equivalent dosage.

Side-effects

The incidence of side-effects was low, and in no instance was it necessary to interrupt therapy. Thirteen patients had moon facies as a result of previous prolonged administration of prednisolone. However, when treatment was continued with Aristocort, there was no increase in this and, in some cases, a decrease in the severity of the moon facies was noted. We cannot state whether the reduction in moon facies was due to the lower dosages of Aristocort as compared to prednisolone or whether this new steroid has less of a Cushingoid effect because of some variation in its metabolic activity. It is well known that patients on prednisolone therapy often develop a voracious appetite. In our series, we observed a decrease of appetite in several individuals. This impression was corroborated by loss of weight observed in 11 of the 26 patients. However, we do not know if this weight loss was due to the decreased appetite or whether there was a reduction in subclinical fluid retention. There were no significant changes in blood pressure observed in this series. Two patients developed gastrointestinal complaints (one transient nausea and the other mild abdominal cramps) which subsided on antacid therapy. Two patients developed a mild acneiform eruption on the face after two weeks of therapy. Headaches and tremors were observed in one woman. She had previously developed similar symptoms when on prednisolone therapy.

One patient with pemphigus erythematosus had received previous therapy with prednisolone with an initial dosage of 60 mg. daily. After seven weeks of treatment, he had developed glycosuria, which persisted when therapy was continued with Aristocort.

TABLE 2.—*Equivalent Doses of Prednisolone and Aristocort Diacetate as Determined in Twenty-six Dermatological Patients*

Case No.	Prednisolone, Mg.	Aristocort Diacetate, Mg.
1	40	30
2	30	20
3	30	20
4	30	16
5	20	12
6	30	20
7	30	20
8	20	12
9	15	8
10	10	6
11	15	8
12	20	12
13	40	32
14	...	Received Aristocort only
15	...	Received Aristocort only
16	40	32
17	15	8
18	15	12
19	15	10
20	15	10
21	20	12
22	20	12
23	20	16
24	25	16
25	15	6
26	15	10

Summary

In a study of 26 patients, the steroid Δ^1 9α-fluoro-16α-hydroxy-hydrocortisone-diacetate (Aristocort diacetate) was proved to have potent anti-inflammatory and antipruritic properties in the treatment of severe dermatoses. It was also observed that Aristocort was more active than prednisolone. No significant side-effects were noted, although a longer period of observation is necessary to evaluate this new corticosteroid compound properly.

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The Aristocort used in this study was supplied by Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

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HYDRALAZINE SYNDROME—HYPERSENSITIVITY OR TOXICITY?

ITS SIGNIFICANCE IN UNDERSTANDING OF COLLAGEN DISEASE

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The occurrence of a syndrome simulating collagen disease during the course of hydralazine (Apresoline, 1-hydrazinophthalazine hydrochloride) therapy was first reported by Morrow, Schroeder, and Perry,[1] in December, 1953. They described a syndrome that appeared in 16 patients after 4 to 23 months of treatment with hydralazine and that was at first indistinguishable from acute rheumatoid arthritis and, if hydralazine administration was continued, systemic lupus erythematosus.

Dustan and others [2] reported a rheumatic and febrile syndrome appearing in 13 of 139 patients during prolonged hydralazine therapy which in its milder phases resembled early rheumatoid arthritis and in its more severe form simulated aspects of systemic lupus erythematosus. Perry and Schroeder [3] reported the appearance of a syndrome simulating collagen disease in 17 of 211 patients on hydralazine therapy. Additional cases have been reported by Manter,[4] Feder,[5] Reinhardt and Waldron,[6] and Shackman, Swiller, and Morrison.[7] Erickson and his associates [8] reported the syndrome in 5 of a group of more than 200 patients who were taking hydralazine for hypertension. Comens [9] produced in dogs a syndrome that resembled systemic lupus erythematosus with dosages of hydralazine approaching the maximum human therapeutic dose.[10] These animals showed clinical, laboratory, and pathological findings resembling those of systemic lupus erythematosus. The L. E. cell was demonstrated in the peripheral blood in seven out of eight animals and hematoxylin bodies in the eighth.

The development of such a syndrome during the course of and, apparently, as a complication of hydralazine therapy, has aroused natural interest and also the hope that an understanding of its mechanism might throw some light on the pathogenesis of systemic lupus erythematosus. The following case report is felt to be of significance in that a syndrome simulating acute rheumatoid arthritis appeared in a patient who had received a comparatively small amount of the drug over a short period of time.

Report of a Case

Since this paper is primarily concerned with the effects of hydralazine, only so much of the case history as pertains to this aspect will be reported.

A housewife, aged 39, was admitted to the hypertension division of the Henry Ford Hospital on Aug. 19, 1955. Her chief complaints were intermittent episodes of acute dyspnea, recurrent headaches, eye aches, and weakness of approximately one year's duration. She had been treated for hypertension previously but had not received "specific" antihypertensive agents. There was no history of drug idiosyncracy and no personal or family history of allergy. One brother had died as a result of hypertensive heart disease.

The significant abnormal physical findings were as follows: blood pressure, 260 mm. Hg systolic, 150 mm. Hg diastolic; grade 3 retinopathy on funduscopic examination; and a persistent tachycardia of 100 beats per minute. The diagnosis of hypertensive cardiovascular disease was established by physical examination, by increased transverse diameter of the heart on x-ray, and by a left ventricular hypertrophy pattern on the electrocardiogram. Renal studies were within normal

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limits with the exception of a hypoplastic but apparently good-functioning right kidney as revealed by intravenous pyelograms. The phentolamine (Regitine) methanesulfonate test was negative.

Because of its bearing on the course and management of this patient, it should be stated that she was extremely uncooperative, was usually acutely disturbed emotionally because of family discord, and, in general, was a most difficult person to deal with.

Antihypertensive therapy was instituted with reserpine. On Sept. 1, 1955, hydralazine, 10 mg. four times a day, was added to her program. However, this was withdrawn after a total of five doses had been given because of increase in tachycardia and rise of blood pressure after administration of the drug. She was discharged Sept. 3 on therapy with sodium amytal, 1 grain (60 mg.) four times a day, and reserpine, 1.5 mg. four times a day. On Sept. 15 she was readmitted to the hospital because of persistent high blood pressure levels and incipient congestive heart failure. Investigation during this admission was directed toward a reevaluation of the cardiac status and a consideration of the possibility of pheochromocytoma.

Treatment during this period revolved around blood pressure control and correction of the congestive heart failure. Because of failure to obtain a satisfactory sustained decrease in blood pressure with reserpine and pentolinium (Ansolysen), hydralazine was added to the program on Sept. 26. This was given in a dosage of 10 mg. four times a day. In addition she was given "repeat action" chlorpheniramine (Chlor-Trimeton Repetabs). At this time there was no unfavorable effect from hydralazine, and on Sept. 30 the dosage was increased to 25 mg. four times a day and the patient was discharged with her condition under fairly good control. She was seen on an outpatient basis on Oct. 12 and again on Oct. 19. She reported no unusual symptoms.

On Oct. 25 she returned and gave the following history: several days previously she had developed a painful, red, nodular swelling on the right forearm which had subsided somewhat prior to the visit. Two days previously, she had developed pain in the left ankle. On physical examination she was seen to walk with a limp, favoring the left ankle. There was swelling of the left ankle joint, with redness and local tenderness confined mainly to the anterior tibial tendon and that region of the dorsum of the joint. There was pain on attempted motion of the joint. There was a pea-sized, freely mobile, firm, tender nodule beneath the skin of the right forearm. It was felt that these symptoms had been caused by hydralazine, and, accordingly, the medication was discontinued. Laboratory studies were requested to further evaluate this situation, but the patient did not cooperate.

She was next seen on Nov. 4 and stated that joint symptoms had completely disappeared over a period of three or four days after hydralazine was withdrawn. Physical examination revealed minimal tenderness in the left ankle. The forearm nodule was still palpable but nontender. She continued as an outpatient until March, 1956. During this entire period control of the hypertension continued to be a difficult problem. During this time also, urine specimens were assayed to determine the amount of pyrocatechin (catechol) amines. These were found to be within normal limits.

On March 19 she was readmitted to the hospital because of acute congestive heart failure, which responded readily to the usual measures. Intravenous pyelograms and serum creatinine levels were normal during this admission. Dosages of reserpine as high as 4 mg. per day and of pentolinium as high as 400 mg. every eight hours, with hospital and home-recorded blood pressure readings as a guide, were insufficient to obtain a satisfactory hypotensive response. Accordingly it was decided to add hydralazine to her program.

On April 10 she was started on therapy with hydralazine, 10 mg. three times a day. On the evening of April 13 the dosage of hydralazine was increased to 25 mg. four times a day. On the morning of April 15 hydralazine was withdrawn. The total amount of hydralazine administered during this period was 235 mg. Tripelennamine (Pyribenzamine) hydrochloride, 50 mg., was given with each dose of hydralazine.

On April 13, when the dosage of hydralazine was increased, the patient started to complain of joint pain in her hands. On the following day her temperature rose to 99.6 F (37.5 C), and she complained of pain and swelling of all the metacarpophalangeal joints of the right hand and of the proximal interphalangeal joint of the left fourth finger. She stated that the joint symptoms were aggravated by her taking her medicaments (which included hydralazine) and that the symptoms subsided between doses and became aggravated by succeeding doses. On examination there was seen to be an acute inflammatory, fusiform swelling of the affected joints. The joints were acutely tender and there was pain on attempted motion.

Hydralazine therapy was discontinued on the morning of April 15. The temperature returned to normal that evening. Joint manifestations subsided completely over the next three days. A peripheral blood L.E.-cell test on April 17 was negative.

The patient died on June 13, 1956. An autopsy was performed. The cause of death was hypertensive heart disease and thrombosis of the left auricular appendage with multiple infarctions. There was hypoplasia of the right kidney. There were no other significant pathological findings.

This patient exhibited an intolerance to hydralazine on first exposure to the drug. This was manifested by tachycardia and rises in blood pressure after the ingestion of the drug. On her second exposure, 25 days later, she at first appeared to tolerate the medication. However, within less than four weeks, with a dosage of 100 mg. of hydralazine per day, she developed symptoms suggestive of an acute rheumatic process, which regressed rapidly after withdrawal of the drug. Her third and final exposure to hydralazine occurred almost six months later, and on this occasion a clinical picture resembling acute rheumatoid arthritis appeared within four days, became progressively worse in the ensuing two days while the patient was still on hydralazine therapy, and regressed promptly after withdrawal of the drug. The total dosage of hydralazine on this occasion was 235 mg.

These relatively small dosages of hydralazine and the duration of therapy are in contrast to the relatively large dosages and prolonged therapy in previously reported cases. In the group of 13 patients reported by Dustan and her collaborators,[2] the mean time of onset of symptoms was 12 months after the start of hydralazine therapy. The average maintenance dose at the time of onset was 640 mg. per day. They did not observe the syndrome in patients followed over a shorter mean period. In the series reported by Perry and Schroeder,[3] the duration of therapy varied from 2 to 32 months, with a mean duration of 12.1 months. The amount of hydralazine taken, prior to onset of symptoms, varied from 25 Gm. to 300 Gm., with a mean total dosage of 171.1 Gm.

The five patients reported by Erickson and his associates [8] had been taking amounts of hydralazine ranging from 200 to 800 mg. daily and developed symptoms after 13 to 21 months of treatment. The other reported cases [11] followed a similar pattern,

in that symptoms appeared from 8 to 18 months after treatment with dosages of 200 to 600 mg. of hydralazine per day. The patient reported by Shackman and associates [7] is of special interest in that symptoms appeared five days after the discontinuance of therapy with hydralazine. The patient had taken hydralazine for a period of nine months on a dosage level of 200 to 300 mg. per day. Five days after hydralazine was withdrawn, she developed a clinical and laboratory picture mimicking acute systemic lupus erythematosus. The positive laboratory findings included a positive serologic test for syphilis and positive L.E.-cell tests on both sternal marrow and peripheral blood. Within one month, there was no clinical or laboratory evidence of the disease.

Comment

Rich,[12] in 1947, suggested that anaphylactic hypersensitivity was the common etiological denominator in such diseases as rheumatic fever, rheumatoid arthritis, periarteritis nodosa, and systemic lupus erythematosus. He emphasized the fact that many of the basic pathological lesions of these diseases were familiar effects of focal anaphylactic reactions.

The question naturally arises as to whether one can consider this collagen disease–like syndrome caused by hydralazine as a hypersensitivity reaction to the drug. The following criteria may be used to differentiate allergic from nonallergic reactions to drugs [13]: 1. There must be a sensitizing dose, i. e., the individual does not react on first exposure to the drug, unless, of course, he has been previously exposed to an immunologically related compound. 2. The allergic response is different from the pharmacodynamic reaction of the drug or from any manifestation which represents simple accumulation. 3. Once sensitivity has occurred, minute amounts of the drug will cause prompt exacerbation. 4. Withdrawal of the drug is followed by remission of the manifestations, although at a variable rate, depending on the degree of sensitivity which has been produced. 5. The sensitivity to the drug persists indefinitely.

It is clear from a review of the clinical features of the reported cases that not all of these criteria are fulfilled in the vast majority of the cases. Dustan and her associates [2] felt that, while the syndrome might represent a variant type of hypersensitive state, the weight of evidence was against hypersensitivity as the etiological mechanism. The fact that the syndrome developed in individuals without noteworthy history of allergic diathesis; that it developed in patients who had taken the drug for long periods; that the dosages used in these individuals were large, in comparison to those in common use; and that one of their patients was able to resume taking the drug at a dosage lower than that which had caused symptoms was felt by them to be evidence against a hypersensitivity reaction. They felt, rather, that the syndrome was a toxic response to the drug as such.

Morrow, Schroeder, and Perry [1] felt that the syndrome represented the production of a new condition by a new agent and that it was better explained as a phenomenon of depletion rather than as one of hypersensitivity. Evidence in favor of a hypersensitivity mechanism as the basis of production of the hydralazine syndrome is meager. Of the reported cases, the one herein reported probably comes closest to fulfilling the conditions previously outlined. The relatively small dosage and the short duration of therapy would appear to be evidence against both the toxicity and the depletion hypotheses. Features of this case which might have a bearing on the apparent hypersensitivity to small doses of hydralazine are the concurrent use of unusually large doses of reserpine and the probable unilateral renal mechanism, from hypoplastic kidney, of the patient's severe hypertensive disease.

Dustan and her colleagues,[2] in distinguishing between the syndrome observed in their patients and that seen in systemic lupus erythematosus, reported transient pulmonary consolidations in two patients. They stated that the process they observed resembled the pneumonic consolidation seen in rheumatic fever. It has been shown that this type of pulmonary lesion occurs not only in rheumatic fever but also in anaphylactic reactions to sulfonamides and in association with anaphylactic periarteritis nodosa.[14] It has also been observed in the lungs of animals killed during experimental serum sickness.[15] These transient pulmonary consolidations have been observed clinically by Harkavy [16] and others [17] in association with bronchial asthma, with periarteritis nodosa, and with angioneurotic edema. Rich regards these transient consolidations as the pulmonary analogues of cutaneous urticaria and purpura.

As yet, no satisfactory evidence has been presented to explain the mechanism of production of this syndrome which so closely mimics rheumatoid arthritis and systemic lupus erythematosus. The thritis and systemic lupus erythematosus. The weight of evidence to date would appear to be against hypersensitivity as the basic mechanism. However, the other proposed mechanisms, i. e., toxicity and depletion, will not adequately explain the case presented in this paper.

Of some practical significance, however, in the light of a real or apparent increase in the incidence of lupus erythematosus, is the fact that a syndrome which for all intents and purposes is identical with lupus erythematosus can be produced experimentally in animals by hydralazine.[9] A similar syndrome has been shown to occur in a small proportion of humans after use of the same drug. The fact that the disease can be reproduced experimentally should open up new fields in the study of the collagen

group of diseases and perhaps may lead eventually to a better understanding of the underlying factors concerned in their production.

Summary

A case of hydralazine syndrome occurred that differed from previously reported cases in that a clinical picture resembling acute rheumatoid arthritis appeared in a patient who had received a comparatively small amount of the drug over a relatively short period of time. It is important to explore the mechanism of production of the "man-made" disease, in order to better understand the pathogenesis of the collagen group of diseases.

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DEATH DUE TO EOSINOPHILIC MYOCARDITIS RELATED TO TRICHINOSIS

REPORT OF A CASE

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Infestation by Trichinella spiralis is considered to be a common disease in the United States, where as high an incidence as 36% [1] has been recorded when painstaking search is made at autopsy for the encysted larvae. However, the mortality must be low. It is estimated at 6% of the reported cases.[2] An accurate figure for these is not immediately available, but it must be appreciably smaller than the actual attack rate estimated from autopsy figures.

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When death does occur, it is due predominantly to involvement of the heart [1], with production of functional impairment leading to heart failure. Herewith is presented a case report on trichinosis with a fatal outcome in which the diagnosis was reached only with examination of the autopsy material.

The patient was a 27-year-old male who had noted the concurrent onset of muscular weakness, cough, chills, and fever approximately one month before admission. Chills and fever were persistent, and weakness was progressive, until the patient became bedridden one week before admission. During this week he had a sore throat, with loss of appetite,

and he noted a few days before admission marked difficulty in swallowing because of weakness. In addition, there was pain in the shoulders and hips and occasional mild generalized headache. Vomiting occurred during the five days prior to admission.

History.—Several times previously, the patient had been admitted to this hospital because of headache and episodes of confusion which were considered typical of psychomotor epileptic seizures. Confirmatory electroencephalograms were available. Other findings during these admissions were constant mild eosinophilia of 4 to 6% and markedly diminished but symmetrical deep tendon reflexes.

Physical Examination.—Physical examination revealed a temperature of 98.6 F (37 C), pulse rate of 100 per minute, and blood pressure 145/80 mm. Hg. The patient was a well-developed, well-nourished, male, breathing rapidly, complaining of marked weakness, and perspiring heavily. There was no nuchal rigidity, and no redness, injection, or exudate were noted in the throat. The lungs were clear to percussion and auscultation. The heart demonstrated regular rhythm with no murmurs or cardiac enlargement. The aortic second sound was louder than the pulmonary second sound. No masses, tenderness, or spasm were present in the abdomen. There was traumatic absence of the right testis. Examination of the extremities revealed muscular weakness, most marked in the lower extremities, but difficult to evaluate because of the patient's inability to cooperate. There was no pain on palpation. Multiple well-healed traumatic scars were present over the right lower extremity. On neurological survey, deep tendon reflexes were all reduced, and the knee jerks were not obtained. Sensory examination showed no abnormalities. No pathological reflexes were obtained. There was no generalized lymphadenopathy.

Laboratory Findings.—The white blood cell count was 14,250, with 56% polymorphonuclear cells, 15% band cells, 12% lymphocytes, 16% eosinophils, and 1% myelocytes. The hemoglobin level was 14 Gm. per 100 cc., the hematocrit reading was 47%, and the corrected sedimentation rate was 30 mm. per hour (Wintrobe method). The urine was yellow-green and acid, with a specific gravity of 1.013, albumin 4+, and no sugar; microscopic examination showed occasional white blood cells. Repeat urinalyses showed essentially the same results with a constant albuminuria. The nonprotein nitrogen level was 75 mg. per 100 cc.; the serum chloride level was 88 mEq. per liter. The Venereal Disease Research Labatory test was nonreactive. A cold agglutination test was negative. Febrile agglutinations to paratyphoid bacillus A and B, Proteus OX-19, and Brucella were negative; positive reactions to typhoid bacillus H and O extended to the third dilution only. A chest x-ray was negative. An electrocardiogram showed sinus tachycardia with a P-R interval of 0.14 sec., QRS interval of 0.12, and Q-T interval of 0.30. Elevation of the ST segments in AVR and AVL with a depression in AVF were noted. The impression was that an intraventricular conduction defect existed. All the precordial leads could not be taken. Serum was subjected to filter paper electrophoresis by the closed-cell method of Durrum and co-workers,[3] stained with bromphenol blue, and analyzed by an analytic densitometer (Analytrol). The examination (fig. 1) revealed that the area representing the alpha$_2$ globulin level was significantly increased to 16% of the total area; the average alpha$_2$ globulin area in our tests was 8.1% ± 1.8%.

Clinical Course.—Throughout his three days' hospital stay, the patient ran a low-grade fever, with temperature elevations to approximately 100 F (37.8C), and he perspired profusely. He complained constantly of weakness and inability to sleep because of generalized aching, particularly about the joints. A lumbar puncture was done, which revealed clear fluid with a protein level of 28 mg. per 100 cc., a chloride level of 122 mEq. per liter, and a sugar level of 100 mg. per 100 cc. On the third hospital day, there was marked and rapid progression of weakness with almost complete paralysis of the extremities. Nasal flaring during inspiration, dyspnea while recumbent, and nasal regurgitation on swallowing occurred. The patient was placed in a Drinker respirator. While he was receiving respirator care a few hours later, his pulse suddenly stopped, and he died.

Findings at Autopsy.—Autopsy was performed 16 hours post mortem, and the following is a résumé of the significant findings: The flabby and dilated heart weighed 350 Gm. No gross changes were noted in the myocardium; however, microscopic examination (fig. 2) revealed a focal disseminated myocarditis consisting of collections of inflammatory cells of which eosinophils predominated. These foci were predominantly between fibrils and in clusters where muscle fibers showed some signs of degeneration with fragmentation and loss of cross-striations.

The right lung weighed 550 Gm.; the left weighed 350. They were slightly congested and showed microscopic evidence of edema. The liver weighed 1,500 Gm. and showed minimal central passive congestion.

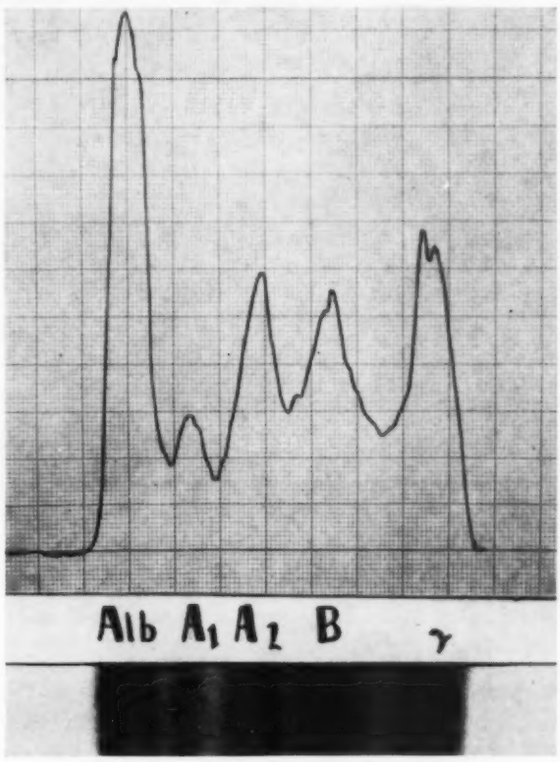

Fig. 1.—Electrophoretic pattern of serum proteins.

The kidneys were unremarkable grossly. Lower nephron nephrosis of moderate degree was detected histologically. No lesions were found on examination of the nervous system including brain, the entire spinal cord, peripheral nerves, and sympathetic ganglions.

Skeletal muscle specimens selected at random, since a diagnosis of primary muscle disease had not been entertained clinically, consisted of portions from the pectoral muscle and extrinsic muscles of the larynx and were unremarkable grossly. On section, however, a striking granulomatous myositis (fig. 3) was present. The exudate, in contrast to that of the myocardium, was predominantly composed of plasma cells and histiocytes with very few eosinophils. There was extensive muscle degenerative change, including loss of striations and loss of staining properties. Swelling and fragmentation of other fibers was a feature. Proliferation of sarcolemmic nuclei was minimal in degree. Some fibers

showed vacuolization. There were no vascular changes of note. In the center of one of the granulomas was found a giant cell with a remnant of a Trichinella.

After evidence of the granulomatous myositis was obtained, a complement fixation test and a bentonite flocculation test for trichinosis were performed on serum obtained during life and kept under refrigeration for about one week at 5 C. The former was negative. The bentonite flocculation test was positive.

Fig. 2.—Focal degeneration of myocardium, with eosinophilic granulocytic response (×450).

Comment

Establishing the diagnosis definitively by finding the parasite in the tissues was not an easy task. One would have expected in the fifth week of illness, as in this case, to find early encapsulation [4] of the larvae; however, none were found. Although there were miliary granulomas in the skeletal muscle sections, extensive search was required before a Trichinella remnant was found in a giant cell. It has been noted that, in human infestation, death of the Trichinella parasite may occur without encapsulation.[1]

The remarkable scarcity of the parasite in any form seems to us to indicate a very considerable maladjustment between parasite and host and a violation of the basic principles of parasitism. Thus, the parasite, inducing a supersensitive response on the part of the host, accomplished the host's extinction and at the same time, its own.

The myocardial lesions are of some interest. It is generally recognized that Trichinella organisms do not encyst in the heart, and, indeed, the larvae or fragments of them are rarely found in the myocardium after the second week.[5] In this case, the eosinophilic granulocytic predominance in the myocardial infiltrate was in striking contrast to the type of inflammatory response in the skeletal muscle. Thus, it appeared that the skeletal muscle lesion was caused by the irritative action of the parasite resulting in a foreign body type of granulomatous reaction. In the myocardium, on the other hand, the lesions were compatible with a supersensitive type of tissue response such as is seen in serum sickness and sulfonamide sensitivity.[6] This speculative interpretation that a disease process may be related to hyperergy may be extended to explain the occasional occurrence of nephritis noted in trichinosis.[7]

The erythrocyte sedimentation rate was significantly increased. Roehm [8] has pointed out that normal rather than increased sedimentation rates usually characterize trichinosis, and he recalled that, in other supersensitive states, the erythrocyte sedimentation rate is frequently normal. However, in the case which Roehm reported, there was a gradual increase from a value of 11 mm. per hour (Wintrobe) early in the course to a high of 30 mm. per hour in the seventh week of illness, the rise coinciding with a development of clinical myocarditis. He felt, therefore, that the presence of inflammation of the myocardium, even though apparently allergic in nature, tends to influence the erythrocyte sedimentation rate. The present case tends to lend support to this concept.

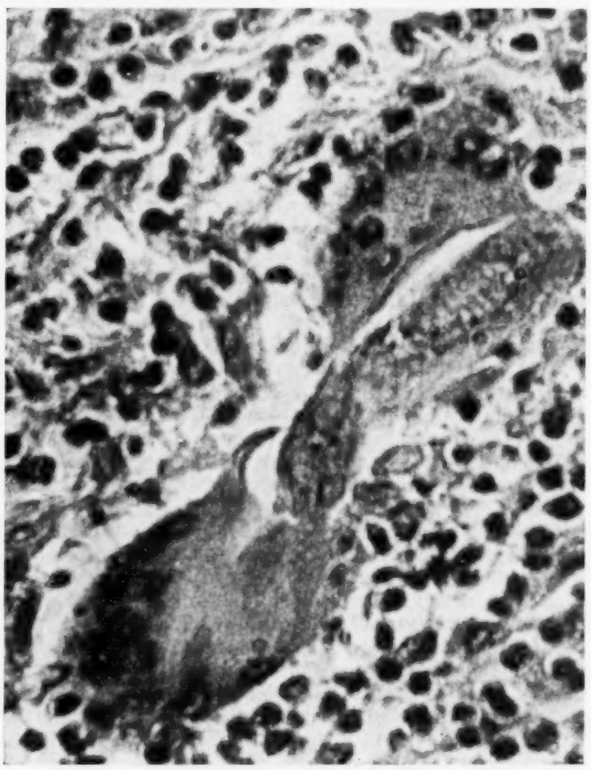

Fig. 3.—Granuloma from skeletal muscle showing a foreign body giant cell about a remnant of Trichinella (×450).

Numerous reports of the coincidence of an increased alpha $_2$ globulin fraction with various diseases have accumulated. A recent review by Jencks and others [9] has called attention to the association of increased alpha $_2$ globulin levels with such diseases as ulcerative colitis, malignancy, nephrosis, and thrombophlebitis. In this laboratory, significant alpha $_2$ increases have been seen in malignancy of varying kinds, including Hodgkin's disease (29 of 32 cases), acute exacerbation of rheumatoid arthritis (3 out of 3), active pulmonary tuberculosis (2 out of 2), ulcerative colitis and ileitis (3 out of 4), and in one case each of psoriasis, nephrosis, asthma, and asthmatic bronchitis, in addition to the present case of trichinosis. Is there a common denominator among this multifaceted collection? It seems that, superficially, at least, one can postulate hypersensitiveness to protein breakdown products as such a common denominator. The demonstration of the relation of rheumatic fever and carditis to hypersensitivity to the Streptococci, the experimental production of glomerulonephritis by injection of antikidney antibodies, and the predominance of eosinophils in the infiltrate in the bronchial walls in asthma and in the exudate about necrotic tumor tissue all tend to strengthen this idea. Thus, an increase in the proportion of the globulin found in the alpha $_2$ area might seem to reflect an anaphylactic quality in the reaction of an organism to injury.

The electrocardiogram, with a widened QRS complex and conduction disturbance, showed evidence of definite myocardial disease in this case. As pointed out by Scherf and Boyd,[10] the electrocardiogram reflects involvement by inflammatory disease of the myocardium most frequently of all clinical tests. Though not always present and by no means specific, the evanescent and recurrent character of the changes seen (usually widened QRS complexes, abnormal T waves, and conduction disturbances [11]) is evidence for myocarditis. In myocarditis associated with trichinosis, at least, this evidence forebodes ill for the outcome.

That the clinical diagnosis of trichinosis was not considered during the brief hospital stay of this patient is hardly reprehensible in view of the lack of a history of ingestion of partially cooked pork and the absence of one of the most frequent signs, periorbital edema. Confronted with a patient complaining primarily of muscular and joint pain with weakness, one is led into the devious maze of differential diagnosis of neuromuscular disorders. As pointed out by Eaton,[12] the tendency is to seek out more diligently the central nervous system disorders resulting in muscular symptoms and to consider polymyositis of one or another etiology last. The symptoms and signs of trichinosis are primarily those of hypersensitivity reaction, which characterize some fifty-odd other disorders. Thus, the diagnosis is by no means simplified. Once the suspicion is aroused, however, skin test with a Trichinella antigen is positive in 90% of the cases.[2] Serologic tests are also available. A complement fixation test is utilized and is reliable but has certain disadvantages. It does not usually become positive until two to five weeks have elapsed, and it is difficult to perform, requiring the use of a specially prepared and standardized reagent and specially trained personnel. Recently, Sadun and Norman [13] have reported on a flocculation test utilizing antigen prepared by adsorption onto Wyoming bentonite of a purified acid soluble protein fraction of Trichinella larvae. Indications are that this test is at least as reliable as the complement fixation test and is much easier to do and read. In addition, it may become positive earlier in the course of the disease. Serologic tests may be more valuable in diagnosis than a muscle biopsy, reflecting as they do the systemic reaction and measuring the degree of hypersensitivity. Generally speaking, the biopsy can only show the parasite and the local reaction to irritation, which might conceivably be an incidental finding related to a previous infestation.

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NUTRITION IN THE SURGICAL PATIENT

MANY SURGICAL patients receive nothing by mouth during the early postoperative period because of either the desire of the surgeon to keep the gastrointestinal tract at rest or anorexia. Such patients should receive nutrition intravenously. One of the commonly used methods of maintaining surgical patients during this period is to give them 2 or 3 liters of either a 5 or 10% sugar solution which may or may not contain some sodium chloride. Such a regimen provides 400 to 1,200 calories; thus it not only is deficient in calories but is devoid of utilizable nitrogen, essential electrolytes (notably potassium), and vitamins. From a nutritional viewpoint it is highly desirable to supply insofar as possible all the essential materials needed for the fabrication of tissue. Otherwise, despite the most skillful surgery, the patient's convalescence will be unnecessarily prolonged and complicated. Rice [1] recommends that, instead of dextrose in a saline solution, the basic fluid for intravenous feeding should contain 20 mEq. of sodium, 15 mEq. of potassium, and 20 mEq. of chloride. To such a solution other elements of nutrition may be added as indicated.

Abbott and co-workers [2] have studied the relation of nitrogen and energy intake to the nitrogen balance in postoperative patients. These were maintained on various levels of intake of both nitrogen and calories during the immediate postoperative period and the five-day cumulative nitrogen balance (the day of operation plus the next four postoperative days) was determined. In this manner it was possible to compare the effects of various nutritional regimens on the cumulative nitrogen balance during a period when nitrogen deficits are ordinarily expected to be large. After a subtotal gastrectomy or hemigastrectomy-vagotomy, male patients who were maintained solely on sugar solutions during the postoperative period showed a five-day cumulative nitrogen deficit of about 60 Gm. and lost about 0.5 kg. (1 lb.) of body weight per day. Female patients undergoing a comparable surgical operation and maintained on a similar nutritional plan showed about half of the nitrogen deficit that was noted in the male patients and they lost less weight.

By giving the postoperative patient solutions of protein hydrolysates containing 10% hexose it is possible to administer about 12 Gm. of nitrogen and 1,100 calories using only 2 liters of fluid. Such preparations contain added potassium as well as some sodium and chloride. It is possible to further increase the caloric content of the regimen by giving an additional amount of the same solution or one containing, in addition, slightly higher concentrations of hexose and 2 to 5% alcohol. The use of protein hydrolysates and sugar solutions provides the suggested [3] energy (40 calories per kilogram) and nitrogen (0.4 Gm. of nitrogen per kilogram) intakes only for persons of small stature who undergo subtotal gastrectomy or an operation of comparable magnitude. For the patient of average size or larger, the fluid intake necessary to carry the caloric and nitrogen needs becomes excessive. However, by using this suboptimal nutritional regimen it is possible to reduce the five-day cumulative nitrogen deficit of male patients with subtotal gastrectomy to 30 or 40 Gm.[4] Thus, by giving nitrogen and calories to patients in the immediate postoperative period, these nitrogen deficits can be reduced by 33 to 50%. From these studies it is evident that the destruction of body tissue can be significantly reduced by giving nitrogen and calories in the postoperative period.

Testosterone propionate has been known to have an anabolic effect when given to experimental animals and man. When 200 to 250 mg. of a long-acting anabolic hormone, testosterone cyclopentylpropionate or 19-nortestosterone cyclopentylpropionate, was given to male patients prior to gastrectomy, five-day cumulative nitrogen deficits of only 10 to 15 Gm. developed in spite of the fact that the patients were maintained on about 12 Gm. of nitrogen and suboptimal amounts of calories. The

use of the anabolic hormone thus reduced the nitrogen deficit in the surgical patient and minimized or prevented weight loss.[2]

To give about 40 calories per kilogram to the average-sized patient by intravenous feeding, it is necessary to use either very hypertonic sugar solutions (25 to 50%), alcohol, or fat emulsions. Interesting experimental studies with the use of fat emulsions are being made,[5] but many problems must yet be solved before this can be considered a practical procedure for routine use. On the other hand, it is a simple matter to add water-soluble vitamins to an intravenous feeding. If after an operation a patient who is slightly deficient in some vitamin is loaded with dextrose solution he may be thrown into an acute attack of scurvy, beriberi, or pellagra unless the appropriate vitamins are given.[6] All undernourished patients to whom large amounts of carbohydrate are to be given should receive supplements of water-soluble vitamins. Spies[6] recommends a daily supplement of 20 mg. of niacin, 7.5 mg. of riboflavin, and 5 mg. of thiamine.

Many seemingly miraculous advances in surgical technique have been made in recent years. If the benefits to the patients are to keep pace with these advances, more attention must be paid to the postoperative maintenance of nutrition. This cannot be done by concentrating on electrolyte balance and supplying sufficient calories. Amino acids and vitamins must also be provided in adequate amounts.

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COMMUNITY COOPERATION

No one truly meets all of his responsibilities by contributing a certain amount of money to a campaign fund. This is especially true for physicians. There are certain medical public relations "jobs," and they can be pleasant, which the physician must do for himself. One of these is constructive participation in community health activities.

People are concerned about their health, and physicians have helped make them that way. The fruit of that effort shows itself in the various medical welfare organizations which have been and are being founded. The ground has been prepared, the seed has been planted, and the profession must not now neglect the harvest. These many community health projects and medical welfare organizations in our midst, without proper supervision, can bring serious criticism—not always on the health project or welfare organization but on the medical profession which has let them go unguided.

Seldom is it that these organizations do not use the names of leading physicians in their work. This is necessary for public support. The physician who lends his name for such purpose without also giving some of his time and attention to observing and directing the organization is doing himself and his profession a great disservice. When physicians offer their services to these groups and show by their daily actions that they are genuinely interested in the public health, they find that the public is ready, willing, and anxious to accept medical guidance.

Patently, the administration and planning within community health organizations must never become the function of nonmedical individuals without the help and advice of responsible physicians who reside in the community. As a practical matter, sometimes physicians are too busy with their own private practice to bother about these organizations until one day one of them does something the physician does not like. Then he may spend hours protesting, making threats of noncooperation, and generally creating a bad impression of himself—and his colleagues. Physicians can and must fulfill their obligations to these groups by attending meetings (even though there are cries today that there are too many meetings) and showing an interest during the formative stages of his fellow citizens' projects.

The practicing physician, by the personal touch in his office and through his county medical society, can guarantee the public quality medical care available at all times plus free choice of physician and recourse against injustice by assuring sound medical advice in all matters relating to improvement of the public health.

ORGANIZATION SECTION

THE NEXT AMERICAN MEDICAL DIRECTORY

The 20th edition of the American Medical Directory for 1958 is now going to press. The new volume, which is expected to be ready for shipping by early September, 1958, will contain over 100,000 changes of address since the 19th edition, with biographical data on 19,000 new physicians. It will also include over 14,000 other changes in specialties and certifications by the Examining Boards for Medical Specialties. The 20th edition will contain complete data on over 260,000 physicians from the United States and Canada.

The publication price for orders paid before Jan. 1, 1958, will be $30 for the United States and Possessions and $33 for outside the United States and Possessions. For orders received and paid after Jan. 1, 1958, the cost will be $35 for the United States and Possessions and $38 for outside United States and Possessions.

Since several hundred orders have already been received, orders should be mailed early to make sure that a copy will be reserved for the purchaser.

WORLD CONFERENCE ON MEDICAL EDUCATION

Dr. Louis H. Bauer, New York, has announced the preliminary program for the second World Conference on Medical Education to be held at Chicago's Palmer House, Aug. 30 to Sept. 4, 1959. "Medicine—a Life-Long Study" will be the theme of this conference, held under the auspices of the World Medical Association. Collaborating organizations will be the World Health Organization, the Council for International Organizations of Medical Sciences, and the International Association of Universities.

The president of the conference will be Dr. Raymond B. Allen, chancellor, University of California in Los Angeles; one of the deputy presidents will be Dr. Victor Johnson, director, Mayo Foundation for Medical Education and Research.

The program for the second world conference will include such areas as basic clinical training for all doctors, advance clinical training for general and specialty practice, training for teaching and research, and continuing medical education. Participants will include leaders in this field from nations throughout the world.

The first such conference, also sponsored by the WMA, was held in London in August, 1953.

NEW BOOKLET ON MEDICOLEGAL FORMS WITH LEGAL ANALYSIS

The A. M. A. has just released a new booklet entitled "Medicolegal Forms with Legal Analysis" which it plans to distribute to physician members of the A. M. A., on request, as long as the supply lasts. Copies are available to attorneys, hospitals, and other interested persons at a cost of $1.00 per copy. Parts of the text of this booklet and a few of the medicolegal forms appeared in a series of six articles published in recent months in Medicine and the Law section of THE JOURNAL.

INDUSTRIAL HEALTH CONGRESS IN MILWAUKEE

A principal topic of consideration at the 18th annual Congress on Industrial Health, Jan. 27-29, at the Schroeder Hotel in Milwaukee, will be maintaining high standards of health in industry. Physicians, nurses, industrial hygienists, engineers, and others interested in the field will attend the meeting sponsored by the A. M. A. Council on Industrial Health.

Recent developments in industrial health programs and various aspects of immunization programs in industry will be among the subjects covered by panelists at a special session co-sponsored by chairmen of state medical society committees on industrial health. Other features will be three technical sessions on (1) general aspects of disability evaluation; (2) industrial dermatitis, causes and evaluation of disability; and (3) low back pain, cause, treatment, evaluation of disability, and rehabilitation.

WINTERTIME FUN

How to live sensibly and still have a good time in cold weather is outlined in a new series of radio transcriptions which the A. M. A. Bureau of Health Education will have available for medical societies early in December. In the 13-program series "The Picture of Health," brief dramatizations of typical family life are presented—illustrating how far the bedroom window should be open at night or the kinds of food one should eat to stay healthy. Other subjects covered include general winter exposures; snow and ice hazards for pedestrians; frostbite and chilblains; skiing hazards; diet; driving; and household procedures (such as temperature and moisture in the room).

NOMENCLATURE INSTITUTES IN 1958

The Nomenclature Institutes have been so popular that the A. M. A. again plans to sponsor two more of these short courses during 1958. The first will be held from March 31 to April 2, at Tulsa, Okla.; the second will be in July, in Boston. These three-day meetings are planned as a special service to medical record librarians and others working with the Standard Nomenclature of Diseases and Operations in the hospital, clinic, or doctor's office. Lectures will be given by Edward T. Thompson, M.D., nomenclature editor, and chief, intermural research activities, division of hospital facilities, U. S. Public Health Service, Washington, D. C., and Adaline C. Hayden, C.R.L., nomenclature associate editor.

Two new members have recently been appointed by the Board of Trustees to the editorial advisory board of Standard Nomenclature of Diseases and Operations. They are Dr. Kenneth Babcock, director, Joint Commission on Accreditation of Hospitals, and Dr. Edwin P. Jordan, executive secretary, American Association of Medical Clinics.

COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

POSTGRADUATE COURSES

The following courses have not been reported previously to the Council on Medical Education and Hospitals.

An intermittent course on the diagnosis and management of cardiopulmonary disease is scheduled by the Yale University School of Medicine to begin Jan. 9 and conclude Jan. 27, 1958, at the Yale–New Haven Medical Center, 789 Howard Ave., New Haven. Using patient demonstration, lecture, and open question periods as methods of education, the course will have eight sessions for two and one-half hours each on Thursdays at a fee of $40. For further information, inquiries should be directed to the Assistant Dean of Postgraduate Medical Education, Yale University School of Medicine, 333 Cedar St., New Haven, Conn.

A four-day continuous course in everyday psychiatry is scheduled for Jan. 9-12, 1958, by Mount Zion Hospital, San Francisco, in cooperation with the San Francisco Psychoanalytical Institute and University of California Medical Extension. The first two days will be devoted to psychiatry in medical practice for general physicians, and the last two days to psychiatry in psychiatric practice with emphasis on psychoanalysis. Methods of education include lectures and group discussions. Further information may be obtained from the Head, Medical Extension, University of California Medical Center, San Francisco 22.

Other postgraduate programs by University of California Medical Extension and not previously listed are as follows: Newborn Medicine, Jan. 13-14; Ophthalmoscopy for Physicians in General Practice and in Pediatrics, Jan. 15-16; Hematology, Jan. 25; Pathophysiology of the Gastrointestinal Tract, Jan. 26-28. Information on these may be secured from the above address.

A multidiscipline course, Principles of Epidemiology, will be offered at the Communicable Disease Center, United States Public Health Service, Atlanta, Ga., Jan. 13-17, 1958, for public health physicians, dentists, veterinarians, nurses, laboratory workers, and other members of the public health team. Further information can be obtained from the Chief, Communicable Disease Center, Public Health Service, 57th Street N. E., Atlanta 23, Attention: Chief, Training Branch.

A one-day six-hour course, Recent Advances in Prosthetics and Amputations, will be offered at the University of Mississippi Medical Center, Jackson, Feb. 28, 1958, in cooperation with the Mississippi Division of Vocational Rehabilitation. Educational methods employed will include patient demonstration, live clinic, lecture, open question, and visual aids. The course is designed for physicians in general practice and in part-time specialty practice. There is no fee. For further information, address the Dean, University of Mississippi Medical Center, Jackson, Miss.

The sixth Postgraduate Course in Diabetes and Basic Metabolic Problems will be held Jan. 22-24, 1958, in Atlanta, Ga., in the auditorium of the Academy of Medicine, Fulton County Medical Society. The three-day course was developed and is sponsored by the American Diabetes Association. It is open to members of the medical profession at a fee of $40 for members and $75 for nonmembers. Educational methods include lectures by leaders in this field, open question periods, and panel discussions. Further information may be obtained from the Executive Director, American Diabetes Association, Inc., 1 E. 45th St., New York 17.

The annual postgraduate Conference in Ophthalmology will be presented March 31-April 4 by the Stanford University School of Medicine, with registration restricted to 30 physicians limiting their practice to ophthalmology or to eye, ear, nose, and throat. Programs and further information may be obtained from the office of the Dean, Stanford University School of Medicine, 2398 Sacramento St., San Francisco 15.

COUNCIL ON MENTAL HEALTH

REPORT ON NARCOTIC ADDICTION

The following article is the second of three parts of the report on narcotic addiction developed by the Council on Mental Health in conjunction with its Committee on Narcotic Addiction on request of the Board of Trustees of the American Medical Association, who, after some preliminary study, had specifically referred the matter to this Council for examination.

The report represents a continuing study of the problem over a period of two and one-half years, during which time meetings were held by the Council and its Committee on Narcotic Addiction with experts in the field representing the federal government agencies responsible for narcotic control, police officials concerned with the problem, representatives of the New York Academy of Medicine who have given considerable thought and time to the study of this problem, a specifically interested member of the American Bar Association, and interested physicians in private practice.

The general feeling of the Council members, as expressed in the report, has been that narcotic addiction should be viewed, much more than it has been in the past, as an illness and that there should be a progressive movement in the direction of treating addiction medically rather than punitively. It is pointed out in the report that the problem of narcotic addiction in Great Britain is considerably less, percentage wise, than it is in the United States and the associated fact that in Great Britain the approach to the narcotic addict is a much more medically orientated one.

This report was first presented to the Board of Trustees at the midwinter meeting in November, 1956, in Seattle, and subsequently referred to the House of Delegates and its Reference Committee on Hygiene, Public Health, and Industrial Health at the Annual Meeting of the Association in New York City in June, 1957. On the recommendation of the Reference Committee, the report was adopted at that time by the House of Delegates.

RICHARD J. PLUNKETT, M.D., *Secretary.*

Importance of Method of Initial Contact with Drugs

There is general agreement that, under current circumstances, proper therapeutic administration of opiates seldom leads to addiction. The so-called medical addicts account for only a small fraction of the total number of patients.[26a] Trial of drugs under illicit circumstances accounts for most cases of addiction. Currently two views are held as to how the initial illicit contact with drugs is made. Some persons, including the proponents of the clinic plans, believe that addiction is chiefly spread by deliberate proselyting by drug peddlers in order to expand the illicit market for narcotics.[32] The opposing view is that socioeconomic and psychiatric factors are far more important.[26a] If a person who possesses the psychological traits of an addict is exposed to the socioeconomic factors associated with addiction he is very likely to try drugs and to become addicted. Recent studies on the epidemiology of addiction support the latter idea and agree that proselyting by peddlers is an unimportant factor in the spread of addiction in the United States and Canada.[33] Association with addicts, curiosity, thrill seeking, and pressure from peers in juvenile groups are far more important factors.

Relationship of Opiates and Addiction to Crime

It is a common popular belief that opiates per se (apart from the phenomenon of physical dependence) directly incite otherwise normal persons to violent assaultive criminal acts, including sexual crimes. This view is not tenable. Opiates are quieting drugs that repress hostile urges, create a passive, dreamy state and depress sexual drives. On the other hand, the opiates are valuable to criminals in other ways. They allay anxiety and, therefore, supply a kind of a "dutch courage" which may be valuable to criminals in the commission of certain acts such as petty thievery. It is particularly important to note that this "dutch courage" is achieved without any great deterioration in mental ability or manual dexterity, such as is induced by alcohol and other drugs. It is well proved that many addicts resort to crime in order to obtain funds for drugs so as to prevent withdrawal symptoms.

Do opiates make criminals, or do criminals use opiates? This is an important question on which diverse views are held.

Law enforcement officers usually state that the majority of addicts were criminal or delinquent prior to addiction. Evidence usually given consists of the police records of incarcerated addicts. Rates of delinquency prior to addiction ranging from 25 to 80% are shown in table 1. Estimates in this table are

TABLE 1.—*Percentage of Addicts with Delinquent Records Prior to Addiction*

Author and Reference	Type of Population Sampled	No. of Individuals in Sample	Percentage of Addicts with Delinquent Records Prior to Addiction
Anslinger[11a]	Persons listed in Bureau of Narcotics Files	200	80
Kuznesof, N.: Probation for a Cure, exhibit 3, pt. 5, Hearings Before Subcommittee on Improvements of Criminal Code, Committee of Judiciary, U. S. Senate, 84th Congress, Washington, D. C., U. S. Government Printing Office, 1955.	Prisoners discharged on probation from Lexington	85	75
Lowry, J. V.: Statement and Exhibits in Hearings Before Subcommittee, Committee on Ways and Means, House of Representatives, 84th Congress, Washington, D. C., U. S. Government Printing Office, 1956.	Prisoners and probationers admitted to Lexington 1955 and 1956	300	30% Convictions
Pescor[25]	Admissions to Hospital at Lexington 1936 and 1937	1,036	25% (Only convictions counted)
Stevenson and others[27]	Addicts in Okalla Prison, British Columbia	100	"Majority"

all based on records of addicts who were in conflict with the law and, therefore, possibly are not representative of all addicts in the United States. On the other hand, one can find statements that most addicts were not delinquent and did not engage in crime prior to becoming addicted. These widely varying opinions may be due to differences in the outlook of the various investigators, the characteristics of the populations of the addicts from which the samples were drawn, and differences in the criteria of criminality prior to addiction. Actually, there is truth in both views. There is no question that unstable antisocial persons have used opiates as long as these drugs have been known, and that such persons will continue to abuse these drugs seems a certainty. It is also true that a proportion of addicts did not engage in criminal pursuits prior to addiction and are not basically hostile, antisocial persons. What one cannot determine at present are the true relative percentages of these two types of persons. Both sides agree reasonably well that the majority of addicts do engage in crime (other than violation of the narcotic laws) after they become addicted in order to support their habits. There is also general agreement that the crimes committed by addicts are usually, but by no means always, crimes against property (theft, pickpocketing, shoplifting, confidence rackets) rather than crimes against the person (assault, murder, rape, and so on).

Current Treatment of Addiction

Since ambulatory treatment of addiction (attempts to withdraw drugs without institutionalization of the patient) was condemned by the American Medical Association in 1921, the policy of the Bureau of Narcotics has been to discourage and to prohibit attempts at this form of treatment. Necessarily, therefore, the initial phases of the treatment of addiction have been carried out in institutions. Most of the available data on treatment comes from U. S. Public Health Service Hospitals at Fort Worth, Texas, and Lexington, Ky. Recently the city of New York established a hospital on North Brother Island in New York City for treatment of youthful addicts.

The federal hospitals are required by law to give priority to addicts, prisoners, and probationers who have been convicted of violations of the federal narcotic laws and have recently been authorized to accept addicts committed by the courts of the District of Columbia. These patients, of course, are all under compulsion and must be kept for the entire duration of their sentences, unless they can be transferred to other institutions. Facilities which remain after federal prisoners, probationers, and District of Columbia cases are cared for are made available to addicts on a voluntary basis. The hospitals, however, have no means of holding these persons against their will. Voluntary patients, therefore, frequently leave the hospital after only a day or two of treatment. Currently there is no federal legislation which permits the federal hospitals to accept and hold addicts committed under state laws.

The treatment program of the federal hospitals consists of withdrawal of drugs, study and evaluation of the patient, physical rehabilitation, vocational rehabilitation, psychotherapy for a selected group, and furnishing of social assistance prior to discharge.

Certain weaknesses are readily apparent in this treatment system. The hospitals must accept all patients who are sent to them by the courts. There is very little chance to select the most favorable cases. Insofar as facilities permit, they must accept all voluntary patients who request treatment. The greatest weakness, however, is the lack of continuing medical and social supervision after discharge for all patients. Voluntary patients leaving the federal hospital have no money, no job, and no place to go.[34] They are very likely to return to the same environment and the same conditions which were partly responsible for their addiction. Local social service agencies are frequently resistant to accepting and helping addicts. Even states that have large concentrations of addicts do not have well-organized programs for post-institutional treat-

ment of addiction. There is no provision for continued psychotherapy. It is small wonder, under these conditions, that the relapse rate is high.

Results of Treatment.—The results of treatment in federal hospitals are largely unknown. Lack of knowledge is largely attributable to the lack of provision for aftercare. Patients in these hospitals come from all over the United States, and to follow them and determine their fate is a formidable and expensive task. Many addicts are roamers and difficult to locate and others do not wish to be contacted. Lack of knowledge of the results of treatment is a very serious matter. Without such data it is impossible to determine the success of the treatment program or to plan intelligently for changing the mode of treatment or to select these patients on whom effort should be concentrated.

TABLE 2.—*Partial Historical Summary on Penalties for Narcotic Law Violations*

Law	Yr. Passed	Penalties
Harrison Narcotic Act Internal Revenue Code Sec. 2550 at Seq. (1946) (Based on Federal Tax Power)	1914	Fine of not more than $2,000 and/or imprisonment for not more than 5 yr. No specifications on minimum sentences (1 yr. and one day general federal minimum) or a suspension, probation, or parole of sentence.
Narcotic Drugs Export and Import Act (Jones-Miller Act) (Based on Federal power to regulate foreign commerce)	1922	Fine of not more than $5,000 and imprisonment for not more than 10 yr. No restrictions on judges as to minimum penalty, parole, probation, or suspension.
Act of Aug. 12, 1937	1937	Penalties under Harrison Law amended as follows: First offense: Fine of not more than $2,000 and imprisonment for not more than 5 yr. Second offense: Fine of not more than $5,000 and imprisonment for not more than 10 yr. Third offense: Fine of not more than $10,000 and not more than 20 yr. No restrictions on judges as to minimum penalties, parole, suspension, or probation.
Public Law 255—82nd Congress (Boggs Amendment)	1951	Amended penalties under both Harrison Law and Narcotic Drug Import and Export Act: First offense: Fine of not more than $2,000 and imprisonment for not less than 2 nor more than 5 yr. Second offense: Fine of not more than $2,000 and imprisonment for not less than 5 nor more than 10 yr. Third and subsequent offenses: Fine of not more than $2,000 and imprisonment for not less than 10 nor more than 20 yr. Parole, probation, and suspension possible only on first offense. Note that this law restricted power of judges.
Narcotic Control Law of 1956 (Daniel-Boggs)	1956	Penalties for violations of Harrison Act, Narcotic Drug Import and Export Act, and Marihuana Tax Act increased as follows: I. Illegal possession: First offense: Fine of not more than $20,000; imprisonment of not less than 2 yr. nor more than 10 yr. Parole and probation possible. Second offense: Fine of not more than $20,000; imprisonment of not less than 5 nor more than 20 yr. Third and subsequent offenses: Fine of not more than $20,000; imprisonment of not less than 10 nor more than 20 yr. II. Illegal sale or conspiracy to sell: First offense: Fine of not more than $20,000; imprisonment of not less than 5 nor more than 20 yr. Second and subsequent offenses: Fine of not more than $20,000; imprisonment of not less than 10 nor more than 40 yr. Sale to minor: For sale to person under 18 by person over 18 years of age, penalty is same as for second offense even though it may be first offense. Parole and probation not possible in this category. III. Illegal importation of narcotics and marihuana: Penalties are same as for illegal sale; possession is evidence of illegal import unless explained to satisfaction of jury. IV. Sale of heroin to juveniles: Amends Narcotic Drug Import and Export Act to effect that sale of diacetyl-morphine (heroin) by person over 18 to person under 18 is punishable by fine of not more than $20,000 and by imprisonment of not less than 10 yr. to life; death penalty possible at discretion of jury. Possession of heroin sufficient proof of illegal importation unless explained to satisfaction of jury. V. Possession of narcotic drugs and marihuana on vessels: Sets up penalties for this offense identical to those for sale (Sec. II above). VI. Use of communication facilities: Sets up penalties of fine of not more than $5,000 and imprisonment for 2 to 5 yr. for using communication facilities to violate or to conspire to violate the narcotic laws. VII. Border crossings: Narcotic Addicts and violators: Addicts and violators of narcotic laws must register when leaving U. S., obtain certificate and surrender it on reentry. Penalty is fine of not more than $1,000 and prison for not less than one nor more than 3 yr.

Hearings Before House and Senate Committees

During 1955 committees of the U. S. Senate [4a] and the U. S. House of Representatives [5a] held extensive hearings dealing with the illicit traffic in narcotics and with problems of treatment and rehabilitation of addicts. After these hearings these committees made reports and recommendations [35] on both questions.

The reports of committees of the U. S. House of Representatives and the U. S. Senate on the illicit traffic and on treatment of addiction were similar. These committees state that the United States has the greatest problem of addiction of any western country. Incidence of addiction has increased since the end of World War II. Addiction is spread from addict to addict. Both committees recommended increased penalties for violations of the narcotic laws and these recommendations have been implemented by Public Law 728, 84th Congress, which provides for a sentence of not less than 2 nor more than 10 years on first offense of illegal possession of narcotics or marihuana against the narcotic laws, 5 to 20 years on second, and 10 to 40 years on third possession or subsequent offenses. In this category, parole or probation is possible on the first, but not on subsequent offenses. For illegal sale or for con-

spiring to sell narcotics or marihuana illegally, penalty for first offense is not less than 5 nor more than 20 years and for subsequent offenses 10 to 40 years. Parole and probation are not allowed in this category. For sale or conspiring to sell to persons under 18, sentences are 10 to 40 years. Sale of, or conspiracy to sell, heroin to a person under 18 is punishable by imprisonment from 10 years to life, or, if the jury so directs, by death. Offenses committed under the provisions of any of the laws on narcotics since 1914 count as previous offenses, even though they were committed prior to enactment of Public Law 728. Table 2 gives a historical summary of penalties since passage of the Harrison Act and table 3 gives a comparison of penalties in the United States with those in other countries. The legislators were obviously strongly influenced by testimony of law enforcement officers, to the effect that severe penalities did reduce the incidence of addiction. The laws also contain a number of provisions designed to make enforcement of the narcotic laws easier, such as permitting narcotic agents to make arrests without warrants under certain conditions. Both committees rejected proposals for legalization of distribution of narcotics by clinics.

The report on Treatment and Rehabilitation of Narcotic Addicts by the Senate Committee [4b] is of special interest. The committee stated that less than 15% of addicts are being successfully cured today; voluntary admission to the federal narcotic hospitals is a loose, hodge-podge procedure without federal or state control or supervision; 75% of voluntary patients leave these institutions against medical advice; state and local treatment facilities are meager and state courts lack authority to commit addicts directly to federal narcotic hospitals; community follow-up or rehabilitation services for the discharged addict patient are virtually nonexistent; no facilities are available for isolating the chronic or "incurable" drug addict.

The senate committee recommended that voluntary commitment to federal narcotic hospitals be abolished and replaced by a civil-type commitment system by either federal or state courts; the Public Health Service would be empowered to accept addicts committed by states on a reimbursable basis, provided that the state satisfy the service that suitable facilities for posthospitalization care have been established; commitment orders should provide for a period of at least three years probation to follow treatment; addicts relapsing on more than three occasions would be subject to a federal or state commitment of indeterminate length; the Public Health Service Act should be amended to authorize divulgence of information relating to narcotic addicts to appropriate federal and state authorities in charge of treatment and rehabilitation of narcotic addicts, and to the federal Bureau of Narcotics; research in addiction should be continued and expanded. These recommendations on treatment have been implemented in part by Public Law 764, 84th Congress, Title I of which amends the District of Columbia commitment law.

Attitude of the American Psychiatric Association

The American Psychiatric Association [30] on June 12, 1956, issued a statement critical of proposals then being considered in Congress relative to drug addiction. The Association said that the bills Congress was considering represented backward rather than constructive approaches to a national attack on drug addiction; that the proposed laws were based on a misconception of the nature of drug addiction as a psychiatric illness, and appeared to proceed mistakenly on the assumption that drug addicts are especially responsible for a substantial number of crimes of violence. The statement further said that the bills discourage or abolish previous flexible provisions for parole, probation, and assignment of addicts to federal hospitals, and thus will impede medical progress that has been initiated under existing legislation. The statement was especially critical of provisions for increasing penalties, making sentences mandatory, for abolishing chances for parole or probation, for reporting names of patients seeking admission to federal hospitals voluntarily to the Bureau of Narcotics, and for not distinguishing between addicts who do not sell narcotics, addicts who sell occasionally to support their own habits, and persons who sell narcotics for profit. Some of the provisions to which the American Psychiatric Association objected were included in Public Law 728 (see above) as finally passed; others were not.

TABLE 3.—*Comparison of Penalties for Narcotic Law Violations in Various Countries*

United States	Canada	England	France
Possession First offense 2-10 yr. Second 5-20 yr. Third 10-40 yr. Sale and importing and possession on vessels First offense 5-20 yr. Second 10-40 yr. Sale to minor 10-40 yr. Sale of heroin to minor 10 yr. to life; death at option of jury Parole and probation possible only on first offense for possession	Possession Summary conviction 6 to 18 mo. Indictment 6 mo. to 7 yr. Trafficking 14 yr. maximum, and, in discretion of judge, whipping. Offenses count under habitual criminal act; on third offense, life possible.	Fine not exceeding £1,000, imprisonment not exceeding 10 yr. Judges have complete discretion.	Fine of 360,000 to 3,600,000 francs and prison from 3 mo. to 5 yr. Penalties double in cases of illegal manufacture or sale to minors.

The President's Interbureau Committee

In 1954 President Eisenhower established a committee consisting of the Secretaries of the Treasury, State, Defense, Health, Education, and Welfare, and the Attorney General, which reviewed the federal government's programs on narcotic addiction. This committee filed its report [17a] on Feb. 1, 1956. It recommended continuing study of the problem within the municipalities and states with consultation, assistance, and instruction to be furnished by federal

agencies. The reports state that each state and municipality with an addiction problem should have a senior law-enforcement official in charge of enforcement of the narcotic laws. States and large municipalities with significant problems should develop appropriate programs of treatment of addiction. States wishing to commit addicts to federal hospitals should be permitted to do so on a reimbursable basis. Federal legislation authorizing this for a limited period should be enacted. The committee felt that there was a need for continuation of the policy of punishment of a severe character as a deterrent to narcotic law violations and recommended increases in maximum sentences for first as well as subsequent offenders. The committee believed that prohibition of probation and parole were essential features of such deterrent laws. The Department of Health, Education, and Welfare seems to have differed with the other departments on severe penalties. HEW proposed that wider latitude be given to the courts by authorizing them to commit certain types of violators for a period of hospital treatment followed by an extended period of conditional release under close supervision by qualified personnel. The types of addicts eligible for this procedure would include (*a*) persons without records of criminal activity or delinquency and not involved in violations of the narcotic laws other than obtaining drugs for their own use and (*b*) addicted drug sellers who sell primarily to support their own habits. HEW seemed to have had no objection to severe penalties for drug sellers who are not addicts, or for addicted sellers who seem to be engaged in this occupation primarily for profit.

Opiate Addiction in Canada

In 1955 a committee of the Canadian Senate [37] conducted hearings on opiate addiction in Canada and rejected proposals for establishment of clinics. In 1956 a preliminary report of an important investigation on drug addiction in British Columbia [27] was issued by the University of British Columbia. A remarkable parallel exists between the situations in the United States and in Canada. Both countries have similar narcotic laws and regulations, and considerable publicity and alarms has arisen in both countries over a purported "epidemic" of adolescent addiction. Plans for providing addicts with drugs have been proposed by medical societies in both countries.

As in the United States, addiction to opiates is statistically a small problem. A count of known addicts revealed a total of 3,212 in all Canada, of which 2,364 were law violators. Almost half of these latter group were located in Vancouver, B. C. Most addicts come from economically deprived urban areas, most have unsatisfactory home lives, and the majority had delinquent records prior to becoming addicted. Heroin is the chief drug in the illicit traffic. Detrimental effects of heroin are far less than has been believed. Many addicts voluntarily abstain from narcotics for varying periods but usually relapse. Though the classic psychiatric disorders, such as psychoses and neuroses, are no more common in addicts than in nonaddicted prisoners, addiction is a complicated physical, psychological, and behavioral reaction and is basically a destructive "escapist" technique, and as such is related to delinquency, suicide, and certain mental disorders.

Dr. Stevenson, director of the British Columbia group, [38] opposes narcotic clinics and feels that such clinics would increase rather than decrease the problem. The British Columbia group [27] recommends that facilities for treatment on a voluntary basis be provided but that these not take the form of special narcotic hospitals of the U. S. pattern. Withdrawal treatment would be carried out under maximum security conditions in mental hospitals or special wards of general hospitals. Rehabilitative treatment would be given in an "open" setting in a special home in Vancouver.

Further recommendations include elimination of mandatory sentences for illegal possession of narcotics (as contrasted with sale) and for the same consideration for parole for offenders against the narcotic laws, as is given to offenders against other laws.

Addiction in England

Proponents of the clinic plans state that the United Kingdom has only a very minor problem of opiate addiction. The difference between the incidence of the problem in the United States and Great Britain is attributed to a difference in the regulations regarding prescriptions for opiates in the two countries. In England it is possible for a physician to maintain an addict on narcotics, under certain circumstances. Because of this, proponents of the clinic plans state that the illicit traffic has never been large in England and no artificial barrier has been imposed between physician and addict, so that most addicts are cured.

The situation in Great Britain was reviewed by Mr. John Walker, United Kingdom delegate to the United Nations Narcotic Commission, in testimony before the Canadian Senate. [39] The international commitments of Great Britain with respect to narcotics are the same as those of the United States and Canada. English laws controlling these drugs are also similar to U. S. and Canadian laws and provide penalties for violations ranging up to a maximal fine of 1,000£ and imprisonment of 10 years. Penalties actually imposed, however, are generally much lighter than in the U. S. and Canada. Mr. Walker stated that addiction is a very small problem in the United Kingdom. Opium smoking among the Chinese in England seems to be dying out, but the extent of opium smoking is actually unknown. Use of marihuana is increasing. About 300 persons addicted to "manufactured" drugs (opium, alkaloids,

and their synthetic equivalents) are known. These 300 addicts to manufactured drugs are managed under a regulation which states that drugs may be given to an addict by a physician when "it has been demonstrated that the patient, while capable of leading a useful and normal life when a certain dose is regularly administered, becomes incapable of this when the drug is entirely discontinued." This particular regulation is the major difference between British and U. S. regulations.

Opponents of the clinic plans object to the conclusion that the difference in the incidence of addiction in England and the U. S. is due only to this difference in the narcotic regulations. Social circumstances are so different in the two countries that the difference in addiction rates could be attributed to sociological factors rather than to any difference in laws and regulations. Accuracy of the figures on addiction in Great Britain has been questioned. The system of checking retail outlets for narcotic drugs is not as thorough in England as in the U. S. and Canada, so that considerable diversion from legal stocks could conceivably occur. Seizures of opium in England are greater on a per capita basis than in the U. S. or Canada.

The Kolb Plan

Recently Dr. Lawrence Kolb has also proposed that narcotics be dispensed to addicts under certain safeguards.[1c] Kolb's reasons differ in some respects from those of the New York Academy of Medicine. He believes that fanatics have created a state of hysteria about narcotics that is leading to a "witch-burning" situation, as evidenced by the very severe laws recently passed by the Congress. Kolb points out that alcoholism is a far larger and more dangerous problem than narcotic addiction and alcoholics are not punished as are narcotic addicts. Opiate addiction does not cause physical deterioration or insanity and does not directly incite to crime; "drug addiction is neither menace nor mortal sin, but a health problem—indeed a minor health problem—when compared with . . . alcoholism. . . ." Heroin is not nearly so dangerous as is believed. The federal narcotic law has had good and bad effects. It has reduced the incidence of addiction but, because of unwise enforcement, physicians prescribing for addicts have been sent to jail and inability to obtain opiates brought illness to many hard-working citizens and this illness cost them their jobs. Physicians advocating narcotic laws did not foresee that they would be bound by police interpretations of the regulations. European countries do not have as restrictive laws as the U. S. and have smaller addiction problems.

Referring to old and new laws, Kolb states: "Existing measures and those which are advocated defy common sense and violate sound principles of justice and penology. There is nothing about the nature of addicts to justify such penalties. . . ."

"A major move in the right direction would be to stop the false propaganda about the nature of drug addicts and present it for what is—a health problem which needs some police measures for adequate control. . . ."

"We need an increase in treatment facilities and recognition that some opiate addicts, having reached the stage they have, should be given opiates for their own welfare and the public welfare, too. . . ."

"A workable solution would be to have the medical societies or health departments appoint competent physicians to decide which patients should be carried on an opiate while being prepared for treatment and which ones should be given opiates indefinitely. . . ."

"The details of a scheme of operation should be worked out by a committee of physicians and law-enforcement officers, with the physicians predominant in authority."

Current Proposals for Legalization of the Dispensing of Narcotics Through Clinics

Proposals for legalization of the dispensing of narcotics to addicts have recently been made in popular publications,[1] medical journals,[3] and legal journals.[2] The most detailed plan was written by the Subcommittee on Narcotic Addiction, Committee on Public Health of the New York Academy of Medicine.[3b] This plan is very similar to that proposed in the Eggston Resolution, so both may be treated together. The discussion which follows will, unless otherwise specified, refer to those particular plans.

The current proposals for legalizing distribution of drugs to addicts bear little resemblance to the so-called clinics which operated between 1919 and 1923. They are being advocated by honest, high-principled persons who are dissatisfied with the current management of this difficult social, legal, and medical problem. The plans being proposed have definite objectives which include abolition of the illicit traffic in narcotics, reduction of addiction, and cure and rehabilitation of addicts. All the plans set up complex safeguards to prevent the abuses which seem to have occurred between 1919 and 1923.

The following reasons are some of those given by the proponents of these plans for changing the current system of the management of narcotic addiction include[32]:

The present system has largely been a failure. Despite the expenditure of large sums of money, addiction, and the illicit traffic in narcotics continue to flourish.

The incidence of addiction, although it cannot be established exactly at present, has certainly increased in comparison with the incidence during the war years of 1938 to 1946.

Results of treatment, as currently constituted, are poor and the relapse rate is high.

Persons favoring these plans believe that addiction is spread chiefly by deliberate proselyting of new addicts by peddlers who are interested in expanding the number of addicts and thereby enhancing their profit.[40]

The addict is considered to be an emotionally sick person but not a criminal. Currently, he is treated as a criminal. Most of the crime associated with addiction is due to the addicts' need to obtain money for drugs.

If addicts were supplied with drugs legally, proponents of the plan feel that the results would be as follows:

The addict would no longer be a criminal and would be more amenable to persuasion to undergo rehabilitation, withdrawal of drugs, and psychiatric treatment.

Illicit traffic would be eliminated because it would no longer be profitable.

Recruitment of new addicts would be prevented because the illicit trade would no longer be profitable. The number of addicts would gradually be reduced by treatment and by death.

Method of Operation of Proposed Plan

The mechanisms of the various plans are similar. The best developed plan is that of the Subcommittee on Narcotic Addiction of the Committee on Public Health, New York Academy of Medicine,[6b] which proposes that clinics attached to general hospitals, which will dispense narcotics to addicts, be established simultaneously all over the United States. They would be open 24 hours daily, seven days a week. Addicts would be registered, fingerprinted, and given identification cards. Safeguards against the addict registering in more than one clinic would be set up. Before addicts are given drugs by the clinics, they would be hospitalized for the purpose of establishing the fact of addiction, for medical and psychiatric evaluation, and for assessment of the "minimum needs for nacotics." What is meant by "minimum needs for narcotics" is not defined, but it probably refers to the minimum amount of opiates needed to prevent the appearance of symptoms of abstinence. After determination of minimal needs for narcotics, addicts would receive this amount from the clinics. The plan of the New York Academy of Medicine indicates that drugs would be given to the addict for self-administration, but no more than two day's supply would be furnished at any one time. The Berger and Eggston[2] plan proposes the use of "depot morphine", which presumably would prevent withdrawal signs for 24 hours. This preparation would not be given to the addict for self-administration but would be administered once daily in the clinic.

Provision is made for readmission of the addict to hospitals for reevaluation of drug needs so that the factor of tolerance can be handled. Addicts detected giving away or selling any or all of their supplies (New York Academy Plan) would be liable to "commitment to a hospital for attempted rehabilitation." What sort of commitment, what sort of hospital, and what sort of rehabilitation is not specified.

In addition to dispensing drugs, the clinics would offer all sorts of medical, psychiatric, social, and rehabilitative services to addicts. Every effort would be made to persuade addicts to undergo withdrawal and rehabilitation.

Current enforcement machinery would be maintained to continue suppression of the illicit market in narcotics.

The details of the plan advocated by Kolb[1e] have not been worked out. It differs from the plan of the New York Academy of Medicine chiefly in that opiates would be prescribed by the addict's individual physician (rather than by clinics) after a committee of physicians has decided that such action was warranted.

Objections to the Clinic Plans

The proposals for legitimizing distribution of narcotics to addicts envisage a system which would be far different from that used during the operation of the "clinics" between 1919 and 1923. They have all been proposed by responsible persons of high standing in the medical and other professions. They are obviously motivated by a desire for a more humane and efficient method of handling a very difficult social, medical, and legal problem. They all propose extensive safeguards designed to prevent the abuses which were alleged to have occurred between 1919 and 1923 and all propose intensive treatment of the addict with a view of "curing" him of his addiction.

The important question is whether these plans would achieve their objectives. Would they eliminate or reduce addiction? Would they eliminate the crime associated with addiction? Would they actually eliminate the illicit traffic, or would they only make things worse and spread addiction?

Many informed persons present very grave theoretical and practical objections to such plans.[41] Supplying an addict with drugs will not alter the personality aberrations or the socioeconomic factors which are partly responsible for addiction. Psychiatrists, experienced in managing addicts, doubt that there would be any great success in persuading addicts to undergo withdrawal and to engage in psychotherapy as long as drugs are supplied to them. A large percentage of addicts are poorly motivated for treatment. They feel that, in the drug, they have the answer to their symptoms. They do not regard themselves as being psychiatrically abnormal and, therefore, are resistant to psychotherapeutic measures. All psychiatrists are familiar with the difficulties in treating psychopaths of the kind that constitute a large proportion of addicts. It would seem unwise in light of lack of knowledge of the etiology and treatment of character disorders for

the medical profession to promise good results in managing such persons by purely medical means alone.

Proposals for clinics seem to be based in part on the idea that, in the United States, addiction is spread chiefly by deliberate proselyting of new addicts by peddlers to expand the illicit narcotic markets. The most careful, the most intensive, and the best controlled sociological studies [28] available contradict this view, and state that association, curiosity, and so on, are far more important factors. If this is correct, it seems unlikely that furnishing drugs to addicts legally will stop the formation of new addicts. It might very well enhance the spread of addiction, since the same social factors which presently are associated with addiction will continue to operate despite the source of the narcotics. The fact that alcohol is available legally does not decrease the interest of the adolescent in this drug. Also, the underworld currently seems to have no great interest in proselyting new addicts. The present illicit market of narcotics seems to be larger than can be adequately supplied with all the drugs that are smuggled. However, if the underworld lost part or all of its present market because of the operation of clinics, the drug rings might well turn to active proselyting to create a new market.

The clinic plans imply that the majority of addicts take drugs primarily to prevent withdrawal symptoms and that the majority of addicts would be content with the minimum quantity of drugs which would achieve this effect. This is doubtful. Most addicts probably take drugs for more reasons than the mere prevention of withdrawal symptoms. The psychologically unstable addict desires a rapid and great alteration in his physiological status. They value this more than mere physiological stability. It seems likely, therefore, that most addicts would supplement the drugs obtained from the clinics with other drugs obtained through the illicit market. In this connection it should be remembered that many addicts take more than one drug. The combination of heroin and cocaine is particularly desired. Since cocaine and marihuana do not produce physical dependence no one proposes that the clinics dispense the drugs. The opponents of the plans state that, even if the illicit market in opiates were abolished, one would expect the illicit market in cocaine and marihuana to continue.

On the practical side, it is obvious that the establishment of clinics all over the United States which would operate 24 hours daily, seven days a week, would be very expensive. It also seems that the New York Academy's plan is somewhat unrealistic, since available data on the distribution of addicts indicate that the main foci of addiction are located in a relatively few large cities. How could one expect states with low addiction rates, such as Minnesota, to underwrite the expense of clinics for addicts? Furthermore, all these services to the addicts are to be furnished at no cost. This would inevitably mean diversion of money from programs dealing with questions of far greater medical importance than addiction.

Possibly only a proportion of addicts would register in the clinics. Many addicts have police records, are wanted for various crimes, and would not wish to be fingerprinted. Other patients would fear the stigma of being labeled an addict. All these persons might continue to patronize the illicit market.

The plan of the New York Academy of Medicine apparently envisages putting drugs into the hands of addicts for self-administration. All experience with addicts indicates that this procedure would be subject to abuse, despite any and all precautions taken, and scandal arising from such abuse would be exploited to the embarrassment of physicians attempting to manage the clinics. Addicts detected giving away or selling part of their supplies would be liable to "commitment to a hospital" for rehabilitation. Opponents of the plans state adequate enforcement of this provision would require as many or more narcotic agents as currently are engaging in enforcing the total prohibition of narcotics. The psychiatric effect of constant surveillance of the addict in order to determine whether he is diverting any of his supply of narcotics is, of course, apparent.

Plans for the clinics also assume that most addicts would cease criminal activities if supplied with drugs. Opponents of the plans admit that it is possible that a proportion of addicts might do this. However, the basically hostile, antisocial psychopath could be expected to continue in his criminal activities regardless of whether or not he is receiving drugs. It should be remembered that certain effects of the opiates—lessening of anxiety without great mental or physical impairment—may be valuable in the commission of certain petty criminal acts. One would expect criminals to attempt to use narcotics and the fact of addiction as a shield for their criminal activities. They would plead that they were emotionally sick people and should be sent to a hospital and not in jail.

Attitudes of Legislative Bodies Toward the Clinic Plans

Proposals for clinics have been rejected by the Canadian Senate,[37] the U. S. Senate,[4b] and the U. S. House of Representatives.[5b] The language of these reports is, to say the least, extremely firm. The U. S. Senate committee's conclusion reads in part as follows: "The subcommittee is unalterably opposed to and rejects the 'clinic plan' proposal for supplying narcotic addicts with free or low-cost drugs. We are opposed to all types of so-called ambulatory treatment. . . . Finally, we believe the thought of permanently maintaining drug addiction with 'sustaining' doses of narcotic drugs to be utterly repugnant to the moral principles inherent in our laws and the character of our people."

References cited in text will appear at end of third article of the series.

MEDICAL NEWS

CALIFORNIA

Fellowship in Metabolic Studies and Endocrinology.—Applications are being received for a one- to two-year research fellowship in metabolic studies and endocrinology at the Donner Laboratory, University of California, Berkeley. Board credit has always been allowed. Courses in the Graduate School may be taken in the basic sciences during the fellowship. Address inquiries to Dr. John H. Lawrence, Director, Donner Laboratory, University of California, Berkeley 4, Calif.

Surgeons Meet in Palm Springs.—The annual meeting of the Southern California Chapter of the American College of Surgeons will be held at the El Mirador Hotel in Palm Springs Jan. 17-19, 1958. There will be 44 papers presented by local doctors and panel discussions on "Dilemmas Encountered at the Operating Table," and "Surgical Disorders of the Thyroid." Guest speakers will include Dr. Warren H. Cole, professor of surgery, University of Illinois, Chicago; Dr. Henry Harkins, professor of surgery, University of Washington, Seattle; and Dr. Frank A. MacDonald, president, California Medical Association.

COLORADO

Joint Meeting in Colorado Springs.—The Colorado Regional Meeting of the American College of Physicians will be held in conjunction with the Colorado Society of Internal Medicine at the Broadmoor Hotel, Colorado Springs, Jan. 17-18. Two panel discussions are planned: Modern Concepts in the Diagnosis and Treatment of Infectious Diseases and Use and Abuse of Tranquilizers and Psychic Energizers. The program includes the following topics by invited speakers:

Comparison Between the Use of Penicillin V and G in Treatment of Group A Streptococcal Infections, Dr. Robert J. Glaser, St. Louis.

Use of Renal Biopsy in Evaluation of Kidney Disease, Dr. Martin P. Hutt, Denver.

Bronchial Veins in Mitral Stenosis, Dr. Morgan Berthrong, Colorado Springs.

Ammonia Metabolism: A Review of the Literature, Dr. James L. Karel, Pilger, Neb.

Practical Aspects of the Exfoliative Cytology of the Lungs and Stomach, Dr. Walter T. Wikle, Denver.

Arsine Poisoning, Dr. Lynn James, Grand Junction.

Serum Lactic Dehydrogenase and Serum Transaminase in Human Leukemia, Drs. Gordon B. Magill, New York City, Felix Wroblewski, Brooklyn, and John S. LaDue, New York City.

A clinical pathological conference will be held the afternoon of Jan. 18. Entertainment includes the annual banquet, Jan. 17, at which the guest speaker will be Dr. Chester Keefer, Wade Professor of Medicine, Boston University School of Medicine. For information, write the American College of Physicians, 4200 Pine St., Philadelphia 4.

CONNECTICUT

University News.—Dr. Edward A. Gall, head, department of pathology, University of Cincinnati College of Medicine, will serve as visiting professor of pathology at Yale University School of Medicine, New Haven, Dec. 11-13, and while in the East, he will moderate a clinical pathologic conference at a meeting of the State Medical Association in Hartford.

ILLINOIS

Chicago

University News.—The second lecture in the series on the Growth of Medicine presented at Northwestern University Medical School will be given by Dr. Leo M. Zimmerman, chairman, department of surgery, Chicago Medical School, on "Surgery in the Ancient World," at 8 a. m., Jan. 14.

Medical History Lectures.—An open meeting of the Society of Medical History of Chicago will be held at the Institute of Medicine Dec. 11, 8:00 p. m. The program includes "The Story of Phlebotomy and Transfusion," by Dr. J. Garrott Allen, professor of surgery, University of Chicago School of Medicine, and "What is the True Symbol of Medicine?" by Dr. Frederick Stenn, assistant professor of medicine, Northwestern University Medical School.

Discussion on Bone Tumors.—The Chicago Orthopaedic Society will present a panel discussion on bone tumors by Drs. Michael Bonfiglio, Iowa City, George W. Changus, Norwalk, Conn., Clinton L. Compere, Chicago, and Robert D. Moseley, Chicago, on Dec. 13, 8 p. m., at the Palmer House. Dr. Compere will serve as moderator. All physicians are cordially invited. For information write Dr. William A. Larmon, Secretary, Chicago Orthopaedic Society, 700 N. Michigan Ave., Chicago 1.

MICHIGAN

University News.—Wayne State University's Board of Governors, at its October meeting, authorized the university to seek funds from the legislature for increasing by two-thirds the size of the entering

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

class at the College of Medicine. In another action the board approved a proposed formal agreement between the University and Children's Hospital of Michigan for a cooperative program in medical education.

Physicians Meet in Grand Rapids.—The fifth annual Michigan regional meeting of the American College of Physicians will be held at the Butterworth Hospital, Grand Rapids, Dec. 7. Nineteen papers are scheduled for presentation, including the following by invited speakers:

Phenprocoumon (Marcumar): An Agent for Long-Term Anticoagulant Therapy, Dr. Edward McC. Priest, Henry Ford Hospital, Detroit.

Diagnostic Value of Renal Biopsy, Drs. Yoshikazu Morita, Detroit, Ivan J. Mader, Hackensack, N. J., Elsie J. Cowsert, Eloise, Mich., A. A. Younes, G. Sosa, Wayne State University College of Medicine, Detroit.

At the banquet Dr. Richard A. Kern, of Philadelphia, president of the college, will present "Some Personal Observations in the Near and Middle East." For information write the American College of Physicians, 4200 Pine St., Philadelpiha 4.

Personal.—Dr. Junios M. Rawlings, of Flint, has been elected a member of the Royal Society of Health of London, England. The election was based on a paper delivered by Dr. Rawlings, in Rome, on "Bio-Chemical Changes of the Body Found in Pulmonary Tuberculosis."——Dr. Harold F. Schuknecht, associate surgeon, division of otolaryngology, Henry Ford Hospital, Detroit, gave the second annual Samuel B. Westlake Lecture at the Jewish Hospital Medical Center, St. Louis, on Dec. 5.——Dr. William D. Robinson, professor of internal medicine, University of Michigan School of Medicine, Ann Arbor, has accepted membership on the National Advisory Arthritis and Metabolic Diseases Council, of the U. S. Public Health Service, Bethesda, Md. Dr. Robinson is a former president of the American Rheumatism Association and a member of the American Federation for Clinical Research.——At a recent meeting in Brussels, Belgium, Dr. Osborne A. Brines, chairman, department of pathology, Wayne State University, became the first American to be elected president of the International Society of Clinical Pathology. Membership in the society represents 23 countries. An international congress is held every three years.

MISSOURI

University News.—The Alpha Pi Chapter of the Phi Delta Epsilon Fraternity will hold its annual Hanau W. Loeb Lecture at St. Louis University School of Medicine, Dec. 12, at 4 p. m., at which Dr. Robert E. Olson, Pittsburgh, will discuss "Myocardial Metabolism in Health and Disease."

Grant for Addition to Medical Center.—The University of Missouri has received a grant of $373,000 from the National Institutes of Health division of the U. S. Department of Health, Education and Welfare for construction of an addition to the new Medical Center to house clinical research facilities of the School of Medicine. The grant, together with about $425,000 which the School of Medicine has available from other sources, will be used to construct a five-story addition to the Medical Sciences Building and also an underground laboratory to house the new 2,000,000-volt Van de Graaff x-ray generator which has been given to the School of Medicine by the Donner Foundation of Philadelphia. University architects have begun plans for the addition to the Medical Sciences Building in order that contracts might be awarded early in the spring of 1958. Plans for the underground laboratory are already almost complete. The university has also received a grant of $100,000 from the Hill–Burton funds for construction of the new Nurses' Dormitory.

NEW YORK

Personal.—Dr. Julius B. Richmond, chairman, department of pediatrics, New York State University College of Medicine, Syracuse, has been appointed chairman of the 1958 Institute on Clinical Teaching of the Association of American Medical Colleges.

Society News.—The New York Allergy Society has elected the following officers for 1957-1958: president, Dr. Leoni N. Claman; president-elect, Dr. Aaron D. Spielman; vice-president, Dr. Louis Sternberg; secretary, Dr. Sheppard Siegal; treasurer, Dr. Joseph H. Fries; and assistant secretary-treasurer, Dr. S. Senior Sack.

Lecture on Forensic Medicine.—Dr. Henry A. Davidson will discuss "Criminal Responsibility" at the Jan. 21 meeting of the Nassau Neuropsychiatric Society at the Meadowbrook Hospital. Dr. Davidson, who is the superintendent at the Essex County Overbrook Hospital in Cedar Grove, N. J., has been past-president of the New Jersey Neuropsychiatric Association, chairman of the Psychiatric Section of the American Academy of Forensic Sciences, and Parliamentarian of the American Psychiatric Association.

Student Wins Second Schering Award.—A second consecutive first prize in the Schering awards contest, a nation-wide competition among medical students for the best papers in each of three branches of medicine, has been awarded to Nathaniel Silon, a senior at Albany Medical College who received $1,000 for his paper on "Recent Trend in Corticosteroid Therapy for Ocular Disorders." The contest, sponsored by the Schering Corporation,

Bloomfield, N. J., is designed to develop writing talent among medical students. Silon also won a first prize in the contest last year with his paper on "Recent Applications of Antihistamines in Medicine and Surgery." He is only the second student in the 18-year history of the awards to win two consecutive first prizes. The 1957 award marks the sixth scholastic prize won by Silon since his enrollment at Albany Medical College.

New York City

Lectures to the Laity.—Dr. Hans Selye, professor and director, Institut de Medicine et de Chirurgie Experimentales, Universite de Montreal, Canada, delivered the first in the 23rd annual series of "Lectures to the Laity," at The New York Academy of Medicine Nov. 13 on "The Stress of Life."

Hospital News.—Dr. Ivan D. Baronofsky, clinical professor of surgery, Columbia University College of Physicians and Surgeons, and chief, department of surgery, Mount Sinai Hospital, will discuss "Cancer of the Colon," Jan. 3, in the schedule of lectures by the Division of Neoplastic Diseases at Montefiore Hospital.

Dr. Blair Receives Award.—John E. Blair, Ph.D., bacteriologist at the Hospital for Joint Diseases, New York City, recently received the 1957 Kimble methodology research award at the Conference of State and Provincial Public Health Laboratory Directors. Dr. Blair's award-winning research pertained to "fingerprinting" different strains of staphylococcus bacteria. The award, $1,000 and an engraved plaque, is sponsored by the Kimble Glass Company, a subsidiary of Owens–Illinois Glass Company, "to give recognition to outstanding contributors of improved procedures in the field of public health."

Dr. Schick Honored.—Dr. Bela Schick, who in 1913 developed a test for determining susceptibility to diphtheria, was guest of honor at a dinner Nov. 20, at the Hotel Pierre, New York City, given by the Business and Professional Associates of the American Jewish Congress. Dr. Schick, now 80 years of age, received the "Annual Award for Service to Mankind." Among the principal speakers was Dr. William Kaufman, of Bridgeport, Conn., of the governing council of the Collegium Internationale Allergologicum, who conferred on Dr. Schick the first honorary fellowship of the society and presented to him a "festschrift," to mark his 80th anniversary last July 16. Dr. Schick is visiting professor of pediatrics at the Bela Schick Department of Pediatrics at the Albert Einstein College of Medicine, and is affiliated with Mt. Sinai Hospital, the Beth-El Hospital in Brooklyn, and the Bronx Municipal Hospital Center. He is presently engaged in research into the cause of premature birth.

PENNSYLVANIA

Guthrie Square in Sayre.—Dr. Donald Guthrie, the "first citizen" of Sayre, Pa., received public recognition of his services to the community when fellow citizens met last month to name a square in his honor. For 47 years he has been surgeon-in-chief of Guthrie Clinic and Robert Packer Hospital and is a former clinic assistant. The local newspaper noted that the honor was "for Dr. Guthrie's skill as surgeon and administrator, for his many contributions to the community and area, and for the deep personal regard in which he is held by many thousands of area residents."

Dr. Mitchell Appointed "Presiding Dean."—Dr. John McK. Mitchell, dean of the School of Medicine at the University of Pennsylvania since 1948, has been appointed Presiding Dean of the university's two medical schools. In his new post, Dr. Mitchell will coordinate the programs of the School of Medicine, where he continues to serve as administrative head, and the Graduate School of Medicine, of which Dr. George B. Koelle is dean. In addition, Dr. Mitchell becomes executive officer of a new Joint Medical Council whose creation was concurrently announced. The council, with Dr. Isidore S. Ravdin as chairman, will advise Dr. Mitchell on educational policy and procedures, and help to integrate more closely the work of the university's medical schools and hospitals. The other members elected to the advisory council are Drs. Henry L. Bockus, Dale R. Coman, William E. Ehrich, Arthur Finkelstein, Herbert R. Hawthorne, Donald M. Pillsbury, Francis C. Wood, and Samuel Gurin, Ph.D. After World War II Dr. Mitchell directed a special study of pediatric education, part of a broad investigation of child health services, for the American Academy of Pediatrics. Shortly thereafter, he was appointed dean of Pennsylvania's School of Medicine. He is president-elect of the Association of American Medical Colleges. Dr. Mitchell was awarded an honorary doctor of science degree by his alma mater, Trinity College, in 1949, an honorary doctor of laws by Temple University in 1951, and a second Sc.D. by Dickinson College in 1953.

Philadelphia

Hospital News.—The 10th annual clinical conference of the Wills Eye Hospital Staff and Society of Ex-Residents will be held in Philadelphia Feb. 20-22 in connection with the 125th anniversary of the founding of the hospital. The Arthur J. Bedell lecture will be delivered by Dr. Paul Chandler Feb. 22. In addition to individual presentations and panel discussions on clinical, surgical, and research

subjects, the scientific program will include special surgical clinics. Social activities include an informal reception and supper Feb. 21. The conference will be concluded with a dinner meeting of ex-residents of the hospital.

Personal.—Dr. Fred B. Rogers, associate professor of preventive medicine and public health, Temple University Medical Center, presented the Boyd Lee Spahr Lecture for the academic year at Dickinson College, Carlisle, Pa., Nov. 15, on "William Wood Gerhard; Pioneer in American Nosography." Dr. Gerhard, a graduate of Dickinson College in 1826, is remembered annually by the William Wood Gerhard Gold Medal of the Philadelphia Pathological Society, awarded for outstanding "zeal in research." Dr. Gerhard first clearly differentiated typhoid from typhus fever in 1837.——Dr. Harry E. Bacon, head, department of proctology, Temple University School of Medicine, lectured on "Ulcerative Colitis, Cancer of the Rectum and Common Afflictions of the Anorectum," Oct. 7-8, at the University of Bahia, in Bahia, Salvador, South America.

WISCONSIN

Activate Respiration Center.—Regents of the University of Wisconsin approved a Medical School faculty appointment recently which will permit activation of a Respirator Center at University Hospitals, Madison. Dr. Arthur A. Siebens, now with the State University of New York, will join the university medical faculty April 1, 1958, as associate professor of pediatrics and physiology and director of the center. Funds were made available to the university in 1956, for establishing the center through a grant of about $51,000, from the National Foundation for Infantile Paralysis, New York City. Acute poliomyelitis cases have previously required transport out of the state to one of 15 respirator centers located throughout the United States. The new center will be located in the Bradley Hospital unit and will include respirators, rocking beds, and other breathing aids.

GENERAL

Special Issue of Bacteriology Journal.—The *Journal of Applied Bacteriology*, normally published biannually, will publish three numbers in 1957. The third issue appearing in December will contain papers read at a special symposium of the Society for Applied Bacteriology held in July, 1957. The subject of the symposium was "Bacterial Spores" and the topics ranged from the anatomy of the spore to work on the propagation of bacteria. Orders for the special issue should be sent to Mr. A. H. Walters, Honorary Publications Manager, Society for Applied Bacteriology, Milton–Deosan Research Laboratory, 64 Wimpole St., London, W. 1.

Doctors as Rotary Officers.—Four physicians are serving as officers of Rotary International, worldwide service organization, for the 1957-1958 fiscal year. Dr. Martin M. Teague, Laurens, S. C., is a Rotary information counselor and a past district governor of Rotary International. The other three doctors are serving as district governors: Drs. Horace L. Dormody, Monterey, and Neslen K. Forster, Pacific Palisades, are governors of Rotary districts in California, and Dr. Carl A. Lincke, Carrollton, is Governor of one of the five Rotary districts in Ohio.

Clinical Scientists Meet in Philadelphia.—The 12th meeting of the Association of Clinical Scientists will be held Dec. 13-15, with headquarters at the Bellevue Stratford Hotel, Philadelphia. A tour is planned for Dec. 13 of the Wyeth Laboratories in Radnor, at which scientific demonstrations and presentations will be made by the laboratory's scientific staff. Six papers will be presented at two scientific sessions to be held at the Jefferson Medical College and the Lankenau Hospital, respectively. Presentation of the annual award will be made to Dr. Frank W. Konzelmann, after which Dr. Konzelmann will give the annual oration. A banquet is planned for Dec. 14, at which a diploma of honor will be awarded to Dr. Claude P. Brown, Philadelphia, and Mr. George Pownall Orr will present "The Voyage of the Welcome." For information, write Robert P. MacFate, Secretary-Treasurer, Association of Clinical Scientists, 54 W. Hubbard St., Chicago 10.

Psychoanalysts Meet in New York City.—The Academy of Psychoanalysis will meet Dec. 8 at the Roosevelt Hotel, New York City. The speakers will be Drs. Leon Salzman, associate professor of psychiatry, Georgetown University, Washington, D. C.; John A. P. Millet, lecturer in psychiatry, Columbia University, New York City; Clara M. Thompson, director, William Alanson White Institute of Psychiatry, Psychoanalysis and Psychology, New York City; Harold Kelman, dean, American Institute of Psychoanalysis, New York City; Paul Hoch, commissioner of mental hygiene, New York State; and May G. Romm, training analyst, Institute of Psychoanalysis of Southern California, Beverly Hills. Chairmen for the morning and afternoon sessions will be Drs. William V. Silverberg, New York City, and Jules H. Masserman, Chicago, respectively. For information, write the Academy of Psychoanalysis, 750 Park Ave., New York 21.

International Congress on Chest Diseases.—The fifth International Congress on Diseases of the Chest, sponsored by the American College of Chest Physicians, will be held in Tokyo, Japan, Sept. 7-11, 1958. The congress which will be presented

under the patronage of the Government of Japan and the Japan Science Council, has been endorsed also by the Japan Medical Association. Scientific papers, panel discussions, fireside conferences, and motion pictures will be presented on the following subjects: radiation hazards, coronary disease, occupational diseases of the chest, chest tumors, tuberculosis, cardiopulmonary function studies, asthma and emphysema, cardiovascular surgery, effect of jet air travel in chest disease, bronchoesophagology, tropical diseases of the chest, etiology of lung cancer, pediatric cardiology and metabolic disorders. Discussions will be simultaneously interpreted into the three official languages for the congress, i. e., Japanese, French, and English. There will be exhibits and visits to medical institutions and hospitals in Japan. A special program is being planned for the ladies. The registration fee for each physician is $25 (U. S. currency) and $10 for each family member accompanying the physician. For information, write: Dr. Jo Ono, Secretary General, Fifth International Congess on Diseases of the Chest, School of Medicine, Keio University, 35, Shinanomachi, Shinjuku, Tokyo, Japan, or Mr. Murray Kornfeld, Executive Director, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11, Ill., U. S.

CORRECTION

Contrast Medium.—In the Foreign Letter from Austria entitled "Aortography in Urology" in THE JOURNAL, June 29, 1957, page 1000, the contrast medium used by Dr. Schimatzek should have read Urografin, a mixture of the sodium and methylglucamine salts of diacetrizoate. This medium is marketed in a concentration of 70%.

EXAMINATIONS AND LICENSURE

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 17-19. Sec., Dr. D. G. Gill, State Office Building, Montgomery 4.

CONNECTICUT:* *Homeopathic.* Derby, Dec. 9. Sec., Dr. Donald A. Davis, 38 Elizabeth St., Derby.

DELAWARE: *Examination.* Dover, Jan. 14-16. *Reciprocity.* Dover, Jan. 23. Dr. Joseph S. McDaniel, Professional Bldg., Dover.

IDAHO: *Examination and Reciprocity.* Boise, Jan. 13-15. Ex. Sec., Mr. Armand L. Bird, 364 Sonna Bldg., Boise.

KENTUCKY: *Examination.* Louisville, Dec. 9-11. Sec., Dr. Russell E. Teague, 620 South Third St., Louisville 2.

MARYLAND: *Examination.* Baltimore, Dec. 10-13. Sec., Dr. Frank K. Morris, 1211 Cathedral St., Baltimore.

MASSACHUSETTS: *Examination.* Boston, Jan. 14-17. Sec., Dr. Robert C. Cochrane, 37 State House, Boston.

MISSISSIPPI: *Reciprocity.* Jackson, December. *Examination.* Jackson, June. Asst. Sec., Dr. R. N. Whitfield, Old Capitol, Jackson 113.

NEBRASKA:* *Examination.* Omaha, June. Sec., Mr. Husted K. Watson, Room 1009, State Capitol Bldg., Lincoln 9.

NEW HAMPSHIRE: *Examination and Reciprocity.* Concord, Mar. 12-14. Sec., Dr. Mary M. Atchison, 107 State House, Concord.

NEW YORK: *Examination.* Albany, Buffalo, New York and Syracuse, Dec. 10-13. Sec., Dr. Stiles D. Ezell, 23 South Pearl St., Albany 7.

NORTH CAROLINA: *Endorsement.* Southern Pines, Jan. 11. Sec., Dr. Joseph J. Combs, Professional Bldg., Raleigh.

NORTH DAKOTA: *Examination.* Grand Forks, Jan. 9-12. *Reciprocity.* Grand Forks, Jan. 12. Sec., Dr. C. J. Glaspel, Grafton.

OHIO: *Examination.* Columbus, Dec. 17-19. Dr. H. M. Platter, 21 W. Broad St., Columbus 5.

OKLAHOMA:* *Endorsement.* Oklahoma City, Dec. 14-15. *Examination.* Oklahoma City, June 3-4. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

OREGON:* *Examination.* Portland, Jan. 15-16. Final date for filing application is December 16. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland 4.

PENNSYLVANIA: *Examination.* Philadelphia, January. Acting Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

SOUTH CAROLINA: *Examination.* Columbia, Dec. 10. Sec., Dr. H. E. Jarvey, Jr., 1329 Blanding St., Columbia.

SOUTH DAKOTA:* *Examination.* Sioux Falls, Jan. 21-22. Exec. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

TENNESSEE:* *Examination.* Memphis, Dec. 18-19. Sec., Dr. H. W. Qualls, 1635 Exchange Bldg., Memphis 3.

UTAH: *Examination.* Salt Lake City, July 9-11. Director, Mr. Frank E. Lees, 324 State Capitol Bldg., Salt Lake City 1.

VERMONT: *Examination and Reciprocity.* Burlington, Jan. 29. Sec., Dr. F. J. Lawliss, Richford.

WASHINGTON:* *Examination.* Seattle, Jan. 13-15. Sec., Mr. Thomas A. Carter, Capitol Bldg., Olympia.

WEST VIRGINIA: *Examination.* Charleston, January. Sec., Dr. Newman H. Dyer, State Office Bldg., No. 3, Charleston 5.

WISCONSIN:* *Examination.* Madison, January. Sec., Dr. Thomas W. Tormey, Jr., 1140 State Office Bldg., Madison.

WYOMING: *Examination and Reciprocity.* Cheyenne, Feb. 3. Sec., Dr. Franklin D. Yoder, State Office Bldg., Cheyenne.

ALASKA:* On application in Anchorage and Juneau. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

GUAM: *Subject to Call.* Act. Sec., Dr. S. F. Provencher, Agana.

HAWAII: *Examination.* Honolulu, Jan. 13-14. Sec., Dr. I. L. Tilden, 1020 Kapiolani St., Honolulu.

PUERTO RICO: *Examination.* San Juan, March 4-7. Sec., Mr. Joaquin Mercado Cruz, Box 9156, Santurce.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

IOWA: *Examination.* Des Moines, Jan.14. *Reciprocity.* Des Moines, Jan. 13. Sec., Dr. Elmer W. Hertel, Waverly.

MICHIGAN: *Examination.* Detroit and Ann Arbor, Feb. 14-15. Sec., Mrs. Anne Baker, 116 Stevens T. Mason Bldg., W. Michigan Ave., Lansing.

OKLAHOMA: *Examination.* Oklahoma City, April 4-5. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

TENNESSEE: *Examination.* Memphis, Dec. 13-14. Sec., Dr. O. W. Hyman, 62 S. Dunlap St., Memphis.

WISCONSIN: *Examination.* Madison, March 29. Sec., Mr. William H. Barber, 621 Ransom St., Ripon.

*Basic Science Certificate required.

GOVERNMENT SERVICES

ATOMIC ENERGY COMMISSION

Special Fellowships in Nuclear Science.—In order to meet the increasing demand for highly trained scientists and engineers in nuclear fields, the Atomic Energy Commission has broadened one of its special fellowship programs to include study through the doctorate level. Fellowships, to be known as the "AEC Special Fellowships in Nuclear Science and Engineering," have been established to provide a total of 150 fellowship grants on a one-year basis to first-year, second-year, and third-year graduate students. The fellowships carry basic stipends of $1,600, $1,800, and $2,000, respectively, with additional allowances for dependents, tuition, and travel. The original program, then called "AEC Special Fellowships in Nuclear Energy Technology," was announced on Oct. 30, 1956, and supported one year of study at the first-year graduate level.

The Oak Ridge Institute of Nuclear Studies will continue to administer the broadened program. The institute also administers for the commission the Special Fellowships in Radiological Physics, the Special Fellowships in Industrial Hygiene, and the Oak Ridge Institute of Nuclear Studies Graduate Fellowship Program.

A fellowship board and the commission will make the final selection of the 1958-59 candidates about March 15, 1958. Applications are open to graduates in chemistry, engineering, mathematics, and physics. Application forms may be obtained from the University Relations Division, Oak Ridge Institute of Nuclear Studies, P. O. Box 117, Oak Ridge, Tenn.

ARMY

Nuclear Training for Medical Officers.—Jan. 1, 1958, is the deadline for applications from Army medical officers who wish to enter the nine-month training course in nuclear medicine sponsored by the Armed Forces Special Weapons Project, to begin July 1. Limited spaces are available for Regular Army medical officers who have a background in physical sciences and mathematics. Early applications are advisable to permit sufficient time for processing.

Students will matriculate first at Reed College, Portland, Ore., for five months of instruction and then attend short courses at Hanford Atomic Works, Richland, Wash.; Sandia Base, New Mexico; and Walter Reed Army Institute of Research, Washington, D. C. Graduates of the course will receive an assignment within the established Army career patterns for nuclear medical officers, including duty tours in biological research, clinical isotope usage, industrial radiology and health physics, and staff assignments in nuclear medicine.

NAVY

Wellcome Award to Captain Ayres.—Capt. William W. Ayres, M.C., was awarded the Sir Henry Wellcome award of the Association of Military Surgeons, at the annual meeting in Washington, D. C., in October, for his report of the clinicopathological aspects and follow-up studies of 18 cases of ependymoma of the cauda equina. The Wellcome award, which was established in 1916 by Burroughs Wellcome & Company, Inc., consists of a medal, a scroll, and a cash prize of $500. Captain Ayres is presently on duty as assistant chief, division of pathology, Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, D. C.

Personal.—Capt. Griffin C. Daughtridge, M. C., chief of radiology service, Naval Hospital, Philadelphia, retired Aug. 1, after more than 26 years of active service.

PUBLIC HEALTH SERVICE

Advisory Committee on Chronic Illness.—Surgeon General Leroy Burney has announced the appointment of a 13-member National Advisory Committee on Chronic Illness and Health of the Aged. The committee is composed of authorities in medical education, geriatrics, physical and industrial medicine, nursing, care of the aged, public health, and public welfare. They will review the medical, social, and economic problems associated with chronic illness and aging and will advise the surgeon general in the development of Public Health Service policy and programs in these fields. The first meeting of the advisory committee was held in Washington, D. C., Oct. 17 and 18.

The members of the committee are Drs. Robert Dyer, chief, division of preventive medical services, California State Department of Health, Berkeley; Michael N. Dacso, director, department of physical medicine and rehabilitation, Goldwater Memorial Hospital, New York City; Kieffer D. Davis, medical director, Phillips Petroleum Company, Bartlesville, Okla.; Wilbert C. Davison, dean and professor of pediatrics, Duke University School of Medicine, Durham, N. C.; Ralph E. Dwork, director, Ohio State Department of Health, Columbus; Henry B. Mullholland, assistant dean, University of Virginia Medical School, Charlottesville; Herbert K. Cooper, Lancaster Cleft Palate Center, Lancaster, Pa.; Miss Emilie G. Sargent, executive director, Visiting Nurse Association of Detroit; Mr. John W. Tramburg, commissioner, New Jersey State Department of Institutes and Agencies, Trenton; Attorney William L. Rutherford, Forest Park Foundation, Peoria, Ill.; Dr. Cecil G. Sheps, executive director, Beth Israel Hospital, Boston; Miss Helen M. Lipscomb, executive director, Chronic Illness Service Center, San Francisco; and Mr. Ben Grossman, director, Drexel Home, Chicago.

DEATHS

Luckhardt, Arno Benedict ⊕ distinguished service professor emeritus of physiology, the University of Chicago, died Nov. 6, aged 72, in Miami Beach, Fla., where he was attending the meeting of the American Dental Association which had awarded him an honorary membership. Born in Chicago Aug. 26, 1885, Dr. Luckhardt studied at Conception (Mo.) College, and at the University of Chicago, where he received his bachelor's degree in 1906, master of science in 1908, and Ph.D. in 1911. The following year he received an M.D. degree from Rush Medical College, Chicago. In 1908 he became an assistant in bacteriology at the University of Chicago, subsequently serving as assistant in physiology, associate, instructor, assistant professor, associate professor, professor, and William Beaumont Distinguished Service Professor in physiology. In 1951 he became consultant for the medical department of the J. B. Roerig and Company. Dr. Luckhardt was past-president of the Chicago Literary Club, the American Physiological Society, and the Federation of American Societies for Experimental Biology, honorary president of the International Anesthesia Research Society, which in 1927 presented him with a scroll of recognition for meritorious research in anesthesia and analgesia, and a member of numerous scientific societies. He was one of the original members of the council on dental therapeutics of the American Dental Association. In recognition of his research, Dr. Luckhardt was elected a foreign member of the Deutsche Akademie der Naturforscher, said to be oldest scientific society, founded in 1652. He was a member of the Phi Beta Pi, Sigma Xi, Phi Beta Kappa, Gamma Alpha, Alpha Omega Alpha, and Theta Nu Epsilon. He received the Alpha Omega Alpha Medal in 1938, the Callahan Memorial Award from the Ohio Dental Association in 1943, and the Certificate of Award from the Walter Reed Society in 1952. In 1947 he was elected "Man of the Year" by Phi Beta Pi, which at one time established the Arno B. Luckhardt Lecture. He received the honorary doctor of laws degree from Conception (Mo.) College in 1933 and doctor of science from Northwestern University in 1934. Dr. Luckhardt's discovery, with Dr. J. Bailey Carter, of the anesthetic properties of ethylene gas, announced in 1923, was a major development which stimulated extensive research in that field. His work on determining the function of the parathyroid glands was an important scientific contribution. His work in a broad area of physiology included also research on the secretions of the stomach and pancreas.

⊕ Indicates Member of the American Medical Association.

Horrax, Gilbert ⊕ Boston; born in Glen Ridge, N. J., April 9, 1887; Johns Hopkins University School of Medicine, Baltimore, 1913; veteran of World War I; from 1919 to 1932 successively assistant, instructor, and assistant professor of surgery at Harvard Medical School, where he was for many years instructor in neurological courses for graduates; past-president of the Society of Neurological Surgeons and the Boston Society of Psychiatry and Neurology; past vice-president of the American Neurological Association and of the Association for Research in Nervous and Mental Diseases; member of the New England Surgical Society, Harvey Cushing Society, Boston Surgical Society, and Phi Delta Theta; fellow of the American College of Surgeons; corresponding member of the Société de Neurologie de Paris; honorary member of the section on neurology of the Royal Society of Medicine of England; member of the founders group of the American Board of Surgery; specialist certified by the American Board of Neurological Surgery, serving as a member from 1942 to 1948; served as senior associate in neurological surgery at the Peter Bent Brigham Hospital; since 1932 in charge of the department of neurosurgery, the Lahey Clinic, and neurosurgeon at the New England Deaconess and New England Baptist hospitals; in 1952 appointed consultant, Murphy Army Hospital, Waltham, and in 1953 chief consultant in neurosurgery for the New England area, Veterans Administration hospitals; a trustee of Lawrence Academy, Groton, Mass., and of the Metropolitan State Hospital, Waltham, Mass.; a member of numerous clubs; on the advisory board, *Journal of Neurosurgery*; received the honorary degree of doctor of science from Williams College, Williamstown, Mass., in 1936 and doctor of laws from Temple University, Philadelphia, in 1955; died in the New England Deaconess Hospital Sept. 28, aged 70, of carcinoma of the lung.

Battenfield, John Young ⊕ Snyder, Texas; born in Pryor, Okla., Oct. 24, 1912; University of Oklahoma School of Medicine, Oklahoma City, 1937; member of the Industrial Medical Association; formerly director of the division of preventable diseases, Oklahoma Department of Public Health; served as medical associate of the National Society for the Prevention of Blindness; past-president of the Oklahoma Public Health Association; veteran of World War II; later a physician in charge with the Firestone Plantation Company at Cape Palmas, Liberia, West Africa; served as director of medical services for the government of Guam; co-owner of the Battenfield–Jones Hospital Clinic; died Sept. 17, aged 44, of acute myocardial infarction.

Cantrell, Roy Foster, Captain, U. S. Navy, Burlingame, Calif.; born in Viola, Ark., Jan. 31, 1897; University of Oklahoma School of Medicine, Oklahoma City, 1928; service member of the American Medical Association; commissioned lieutenant (jg) in the medical corps of the Navy on June 5, 1928; subsequently advanced in rank to that of captain, to date from July 20, 1943; during his more than 29 years service, served with the Navy Medical Department throughout the United States and abroad, and on board ships of the fleet; his last assignment was as commanding officer of the U. S. Naval Dispensary, San Francisco; died in the Naval Hospital, Oakland, Oct. 1, aged 60, of infarction of the myocardium.

Keil, Frank Conrad ✦ New York City; born in New York City July 13, 1884; Cornell University Medical College, New York City, 1907; formerly clinical professor of ophthalmology at the New York College of Medicine; specialist certified by the American Board of Ophthalmology and the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the New York Academy of Medicine; honorary police surgeon; veteran of World War I; consulting ophthalmologist, Kings Park State Hospital in Kings Park, Pilgrim State Hospital in West Brentwood, St. Clare's and Manhattan Eye Ear and Throat hospitals; died Oct. 15, aged 73, of coronary occlusion.

Riordan, Timothy Joseph ✦ New York City; born in New York City March 14, 1895; Fordham University School of Medicine, New York City, 1918; specialist certified by the American Board of Dermatology and Syphilology; associate clinical professor of dermatology and syphilology at New York University College of Medicine and the New York Post-Graduate Medical School; member of the American Academy of Dermatology and Syphilology; veteran of World War I; associated with Lutheran, New York Foundling, St. Elizabeth's and Bellevue hospitals in New York City, Bayonne (N. J.) Hospital, and St. Joseph's Hospital in Yonkers, N. Y.; chief attending dermatologist at St. Vincent's Hospital, where he died Sept. 17, aged 62.

Wilson, Archer Alexander ✦ Charleston, W. Va.; born in Cluster Springs, Va., Nov. 23, 1894; Medical College of Virginia, Richmond, 1923; specialist certified by the American Board of Neurological Surgery; past-president of the Kanawha Medical Society; veteran of World War I and for several years chairman of the local medical advisory board to the Selective Service; member of the Congress of Neurological Surgeons and the Harvey Cushing Society; fellow of the American College of Surgeons; chief of the neurological service and a member of the board of trustees at the Charleston General Hospital, which in 1955 presented him with a bronze plaque for his outstanding work in his specialty field; died Sept. 28, aged 62, of cancer.

Dinsmore, Robert Scott ✦ Cleveland; born in Troy, Kan., Aug. 10, 1892; Washington University School of Medicine, St. Louis, 1917; veteran of World War I; member of the founders group of the American Board of Surgery; chairman, 1936-1937 and vice-chairman, 1934-1935, Section on Surgery, General and Abdominal, American Medical Association; past-president of the Cleveland Academy of Medicine and the American Surgical Association; member of the Southern Surgical Association; fellow of the American College of Surgeons; served as senior consultant in surgery, Cleveland Clinic Hospital, where he died Sept. 24, aged 65, of cerebral hemorrhage.

Rabinoff, Sophie ✦ New York City; Woman's Medical College of Pennsylvania, Philadelphia, 1913; specialist certified by the American Board of Preventive Medicine; professor emeritus of preventive medicine, public health and industrial hygiene at the New York Medical College, Flower and Fifth Avenue Hospitals; fellow of the American Public Health Association; served as district health officer at the East Harlem Health Center, Tremont Health Center, and Fordham–Riverdale districts, the Bronx; formerly editor of the public health section, *Medical Woman's Journal*; died in the Flower–Fifth Avenue Hospitals Oct. 2, aged 69, of glioblastoma multiforme.

Barker, William Edward Jr. ✦ Plaquemine, La.; Tulane University School of Medicine, New Orleans, 1917; past-president of the Louisiana State Medical Society; member of the Southeastern Surgical Congress; fellow of the International College of Surgeons and the American College of Surgeons; veteran of World War I; past-chairman of the state board of institutions; a member of the governor's Committee on Mental Health Training and Research; associated with the Plaquemine Sanatorium; past-president of the Plaquemine Rotary Club, of which he was a charter member; died Oct. 4, aged 62.

Greene, Clarence Sumner ✦ Washington, D. C.; Howard University College of Medicine, Washington, D. C., 1936; associate professor of surgery at his alma mater, where he was head of the department of surgery and chief of the division of neurosurgery; certified by the National Board of Medical Examiners; specialist certified by the American Board of Surgery and the American Board of Neurological Surgery; fellow of the American College of Surgeons; associated with Clinical Center, National Institutes of Health in Bethesda, Md.; on the staff of the Freedmen's Hospital, where he died Oct. 9, aged 53, of acute myocardial infarction.

Campbell, Albert James ✱ Sedalia, Mo.; University of Missouri School of Medicine, Columbia, 1904; member of the American Academy of General Practice; for many years registrar of vital statistics of Pettis County; veteran of World War I; served on the Selective Service Board during World War II; past-president of Pettis County Tuberculosis Association; surgeon for the Missouri Pacific Railroad; associated with Bothwell Hospital, where he died Sept. 29, aged 81, of chronic bronchitis, auricular fibrillation, and embolism.

Dingman, Harold Williamson, Chicago; University of Toronto Faculty of Medicine, Toronto, Ontario, Canada, 1905; Grand Rapids Medical College, Grand Rapids, Mich., 1906; member of the Association of Life Insurance Medical Directors of America; veteran of World War I; at one time practiced in Grand Rapids, where he was on the staff of Butterworth Hospital; vice-president and formerly medical director of the Continental Assurance Company; died Sept. 30, aged 73, of coronary insufficiency and arteriosclerosis.

Merrill, George Adams ✱ Brooklyn; Columbia University College of Physicians and Surgeons, New York City, 1905; specialist certified by the American Board of Internal Medicine; served on the faculty of the Long Island College of Medicine; fellow of the American College of Physicians; member of the American Academy of Allergy; served in various capacities on the staffs of the Kings County, Caledonian, and Brooklyn Eye and Ear hospitals, and the Methodist Hospital, where he died Sept. 27, aged 74.

Puckett, Carl ✱ Oklahoma City, Okla.; St. Louis College of Physicians and Surgeons, 1905; specialist certified by the American Board of Preventive Medicine; member of the American Trudeau Society; veteran of World War I; state health commissioner from 1924 to 1927; managing director of the Oklahoma Tuberculosis Association; at one time superintendent of public health of Mayes County; fellow of the American Public Health Association; died in St. Anthony Hospital Sept. 27, aged 74, of coronary occlusion.

Ross, Alonzo Alverly ✱ Lockhart, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1896; past-president of the State Medical Association of Texas; member of the House of Delegates of the American Medical Association from 1930 to 1933 and from 1935 to 1940; served as chairman of the board of health; for many years member of the school board, serving 25 years as chairman; chairman of the Selective Service Board for Caldwell County during World War I; died Sept. 24, aged 89.

Cliff, Benjamin Franklin ✱ Benson, N. C.; George Washington University School of Medicine, Washington, D. C., 1908; veteran of World War I; past-president of the Henderson County Medical Society, Transylvania County Medical Society, and the Johnston County Medical Society; served on the staffs of the Johnston Memorial Hospital in Smithfield and the Dunn (N. C.) Hospital; died in the Mount Alto Hospital, Washington, D. C., Sept. 30, aged 81, of carcinoma of the prostate.

Sophian, Abraham ✱ Kansas City, Mo.; Cornell University Medical College, New York City, 1906; specialist certified by the American Board of Internal Medicine; chief, department of preventive medicine, New York City Health Department Laboratories from 1910 to 1912; at one time associated with the Rockefeller Foundation in New York City; for many years affiliated with the Kansas City General and Menorah hospitals; died in Miami, Fla., Sept. 19, aged 71, of arteriosclerotic heart disease.

Allgeyer, Ernest Emile ✱ New Orleans; Tulane University of Louisiana School of Medicine, New Orleans, 1917; died in the Touro Infirmary Sept. 27, aged 62.

Arntzen, Julius Leo, Tucson, Ariz.; George Washington University School of Medicine, Washington, D. C., 1906; veteran of World War I; for many years associated with the Veterans Administration; died Oct. 1, aged 83, of aneurysm and myocardial hypertrophy.

Aronstam, Noah E. ✱ Detroit; Michigan College of Medicine and Surgery, Detroit, 1898; served as professor of dermatology and venereal diseases at his alma mater; died Sept. 30, aged 85.

Beppler, Paul Hazen ✱ Pullman, Wash.; Jefferson Medical College of Philadelphia, 1925; served as president of the Whitman County Medical Society; veteran of World War I; associated with Pullman Memorial Hospital, where he was first president of the medical staff; served as director of medical service, Washington State College; died Sept. 20, aged 58, of coronary disease.

Brunner, Benjamin Jr. ✱ Wamego, Kan.; University of Kansas School of Medicine, Kansas City, Kan., 1936; associated with Genn Hospital, where he was president of the staff; died Sept. 29, aged 45, of myocardial infarction.

Conrad, Horace Wendell, Guthrie, Okla.; Eclectic Medical Institute, Cincinnati, 1890; Louisville (Ky.) National Medical College, Medical Department State University, 1891; died in the Park Sanitarium Sept. 7, aged 93.

Corio, George Albert ✱ Trenton, N. J.; Georgetown University School of Medicine, Washington, D. C., 1924; past-president of the Mercer County Medical Society; city physician; Trenton area physician for

the New Jersey Athletic Commission during boxing and wrestling contests; associated with St. Francis Hospital; died Sept. 28, aged 58, of pneumonia.

Dady, Elmer Eugene ✠ Minneapolis; Milwaukee Medical College, 1910; a member of the staff at Deaconess Hospital; died Sept. 27, aged 72.

Drummond, Clarence Coombs, Medford, Ore.; Lincoln (Neb.) Medical College of Cotner University, 1896; for many years a missionary in India; at one time associated with Norfolk (Neb.) State Hospital; died Sept. 25, aged 90, of cerebral hemorrhage.

Frank, Jacob William, Drexel Hill, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1905; professor emeritus of roentgenology at his alma mater; specialist certified by the American Board of Radiology; served on the staff of the Hahnemann Hospital; died Oct. 3, aged 84.

Fraser, Samuel ✠ New Boston, N. H.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1904; past-president of the Hillsborough County Medical Society; for many years on the staff of the Moore General Hospital, Goffstown, where he died Sept. 29, aged 79.

Garber, Jerry M. ✠ Mansfield, Ohio; Western Reserve University Medical Department, Cleveland, 1895; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; associated with the Mansfield General Hospital, where he died Sept. 30, aged 85.

Gillespie, Charles Elverton ✠ Seymour, Ind.; Central College of Physicians and Surgeons, Indianapolis, 1901; past-president of the Indiana State Medical Association; veteran of World War I; associated with Jackson County Schneck Memorial Hospital; died Sept. 23, aged 80, of arteriosclerosis.

Gunz, Abraham Nathan, Lindstrom, Minn.; University of Minnesota Medical School, Minneapolis, 1904; veteran of the Spanish–American War; served as chairman of the Chisago County Board of Health and as county coroner; died in the Veterans Administration Hospital in Minneapolis Sept. 19, aged 78, of cholelithiasis.

Holm, Augustus ✠ Moline, Ill.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1901; member of the Michigan State Medical Society; for 50 years practiced in Le Roy, Mich., where he was for many years president of the school board; died Sept. 15, aged 85, of uremia and bleeding duodenal ulcer.

Holmes, Andrew Byron ✠ Fairmont, N. C.; Jefferson Medical College of Philadelphia, 1910; past-president of the Robeson County Medical Society and of the Fifth District Society; veteran of World War I; on the staff of the Robeson Memorial Hospital in Lumberton, where he died Sept. 16, aged 68, of dissecting aneurysm.

Keever, Kenneth William ✠ Magnetic Springs, Ohio; Jefferson Medical College of Philadelphia, 1934; medical director of the Magnetic Springs Rehabilitation Center; on the staff of Union County Memorial Hospital; died in San Antonio Hospital, Kenton, Oct. 9, aged 51, of coronary thrombosis.

Keil, Peter Augustus ✠ Brooklyn; Long Island College Hospital, Brooklyn, 1902; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; director of the Nassau Savings and Loan Association; associated with the Lutheran Hospital, where he died Oct. 13, aged 78, of acute monocytic leukemia.

Keller, Daniel Casteel ✠ Cuyahoga Falls, Ohio; St. Louis University School of Medicine, 1913; died in the City Hospital, Akron, Sept. 21, aged 77.

Kindleberger, Charles Poor, Rear Admiral, U. S. Navy, retired, Coronado, Calif.; University of Pennsylvania Department of Medicine, Philadelphia, 1894; service member of the American Medical Association and in 1930 a Navy representative of the House of Delegates; entered the Navy in 1894 and retired in December, 1934; fellow of the American College of Surgeons; died in the Coronado Hospital Aug. 28, aged 86, of heart disease.

Krakowski, Julian Peter ✠ Camp Point, Ill.; Chicago Medical School, 1926; died in the Blessing Hospital, Quincy, Sept. 7, aged 66.

Lavine, George Robert ✠ Rochester, N. Y.; Albany (N. Y.) Medical College, 1929; certified by the National Board of Medical Examiners; member of the American Psychiatric Association; veteran of World War II; associated with Strong Memorial, Rochester General, Highland, and Rochester State hospitals, and the Monroe County Infirmary; killed in an automobile accident Sept. 27, aged 54.

Levy, Lewis Harris, New Orleans; Tulane University of Louisiana School of Medicine, New Orleans, 1913; member of the Louisiana State Medical Society and the American Academy of General Practice; served in France during World War I; associated with Touro Infirmary; died Sept. 13, aged 68, of coronary attack.

Linn, Wilbur N. ✠ Oshkosh, Wis.; the Hahnemann Medical College and Hospital, Chicago, 1900; died July 16, aged 89, arteriosclerosis.

Lowrey, John McPherson, Surgeon, U. S. Public Health Service, retired, Baltimore; College of Physicians and Surgeons, Baltimore, 1897; veteran of

World War I; service member of the American Medical Association; associated with the U. S. Public Health Service from 1919 to 1938, when he retired; died Aug. 17, aged 83, of bronchopneumonia and arteriosclerosis.

Lyons, Carmine Keith, Charleston, W. Va.; Duke University School of Medicine, Durham, N. C., 1946; certified by the National Board of Medical Examiners; formerly an officer in the U. S. Naval Reserve; served as part-time county health officer; died Oct. 14, aged 35, of a heart attack.

McCall, William K. ✦ Laddonia, Mo.; Barnes Medical College, St. Louis, 1897; served as coroner of Audrain County and as a member of the Laddonia School Board; associated with Audrain County Hospital in Mexico; died in St. Joseph's Hospital, Kirkwood, Sept. 27, aged 81, of hypernephroma of the right kidney.

McDermott, Joseph Anthony ✦ Seattle; Creighton University School of Medicine, Omaha, 1940; veteran of World War II; served on the staff of the Providence Hospital; a surgeon with the Union Pacific Railroad; died Oct. 2, aged 47.

McDonald, William Joseph, Intervale, N. H.; Harvard Medical School, Boston, 1899; veteran of World War I; formerly associated with University Hospital in Iowa City, Iowa; died in the Memorial Hospital, North Conway, Sept. 19, aged 84, of cerebral hemorrhage.

McLean, Alexander David, Menlo Park, Calif.; Hospital College of Medicine, Louisville, Ky., 1895; veteran of World War I; died in the Veterans Administration Hospital, Oakland, Oct. 7, aged 90.

Meiner, Joseph Aaron ✦ Kokomo, Ind.; St. Louis University School of Medicine, 1905; died Sept. 1, aged 77, of cerebral hemorrhage.

Myles, Leo Thomas ✦ Cambridge, Mass.; Tufts College Medical School, Boston, 1904; served on the faculty of his alma mater; at one time chairman of the board of health; for many years medical examiner in Middlesex County; a director of the Cambridge Federal Savings and Loan Bank; associated with St. Elizabeth's Hospital in Boston, Holy Ghost Hospital, and the Cambridge City Hospital, where he died Sept. 24, aged 79.

O'Brien, James William, Oakland, Calif.; Cooper Medical College, San Francisco, 1904; formerly practiced in Sacramento, where he was on the staff of the Mercy Hospital; died Oct. 4, aged 76.

Poirier, Ralph Alexander ✦ Detroit; St. Louis University School of Medicine, 1942; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons and the International College of Surgeons; on the staff of Mount Carmel Hospital; died in Birmingham, Mich., Sept. 28, aged 40.

Rice, Edgar Eugene ✦ Shawnee, Okla.; Northwestern University Medical School, Chicago, 1925; fellow of the American College of Surgeons; in 1911 member of the House of Delegates of the American Medical Association; served as chief of staff, Shawnee City Hospital; on the editorial board of the *Journal of the Oklahoma State Medical Association*; died Sept. 28, aged 58, of coronary thrombosis.

Rodenberg, Albert Henry, Cincinnati; Eclectic Medical College, Cincinnati, 1923; for many years a physician with the city board of health; died in the Veterans Administration Hospital, Lexington, Ky., Sept. 30, aged 63.

Stauffacher, Charles John, Inhambane, Mozambique, Africa; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1912; medical missionary; died Aug. 29, aged 80.

Stewart, Donald Leonidas, Los Angeles; College of Physicians and Surgeons, Boston, 1904; for many years practiced in Atchison, Kan.; died Sept. 19, aged 78, of chronic hypertensive cardiac disease.

Swan, George Forney ✦ Cambridge, Ohio; Ohio State University College of Medicine, Columbus, 1918; fellow of the American College of Surgeons; veteran of World War I; associated with the Guernsey Memorial Hospital; died Sept. 26, aged 68, of coronary thrombosis.

Thomas, Charles Everett ✦ Leesburg, Ind.; Fort Wayne (Ind.) College of Medicine, 1900; died in the Murphy Medical Center, Warsaw, Sept. 22, aged 82, of cerebral hemorrhage.

Thomson, William ✦ Cypress, Ill.; Barnes Medical College, St. Louis, 1909; veteran of World War I; died Sept. 23, aged 74, of coronary thrombosis.

Turkel, Henry Lewis ✦ New York City; Albany (N. Y.) Medical College, 1923; member of the American College of Allergists; adjunct professor of medicine at the New York Polyclinic Medical School and Hospital; on the staff of the Lenox Hospital, where he died Oct. 6, aged 60, of myocardial infarction.

Vander Laan, John Edwin ✦ Muskegon, Mich.; Harvard Medical School, Boston, 1940; specialist certified by the American Board of Internal Medicine; veteran of World War II; associated with Hackley and Mercy hospitals; killed in a plane crash Sept. 27, aged 42.

Walker, Joseph J., Roswell, N. M.; St. Louis College of Physicians and Surgeons, 1908; died Sept. 25, aged 74.

FOREIGN LETTERS

BRAZIL

Portal Hypertension.—Dr. Adonis Carvalho (*Revista da Associação medica brasileira*, vol. 3, Aug., 1957) reported a series of 10 patients with portal hypertension treated by a surgical technique proposed by Dr. Joaquim Cavalcanti in 1954. It consists essentially in splenectomy complemented by ligature of the inferior mesenteric vein and gastric vein. Good immediate results were noted in all patients so treated.

Rh Factor and Mental Deficiency.—Arruda and Barbieri (*Pediatria prática*, vol. 28, July, 1957) reported the results of their studies on the mother-fetus blood incompatibility in 128 children whose IQ varied between that of the imbecile and that of the moron. The series was divided in three groups: (1) patients with a definite etiological diagnosis, (2) patients without an etiological diagnosis, and (3) mongoloids. The A-B-O blood groups and the Rh-factor of the mothers and children were determined. The authors concluded that a hemolytic disease of the child was a cause of the mental deficiency in association, however, with the characteristic neurological findings. They suggest that complete blood transfusion might prevent the mental deficiency in such children.

Nonpainful Delivery.—Salles and Barros (*Revista de gynecologia e d'obstetricia*, vol. 51, June, 1957) reported their results with Read's psychoprophylactic method in the preparation of 72 mothers for delivery. The prenatal classes have access to the services of a full-time psychiatrist. The best results are secured with the women who have good emotional control. A great improvement is obtained after classes and interviews with the psychiatrist. At the first session, 79% of the prospective mothers were classified as being in medium or bad emotional equilibrium. After psychotherapy only 26.3% of them were so classified. Patients who required analgesics or forceps for the shortening of labor were considered failures, although in the reports of some other authors, patients requiring analgesics were not considered failures. In this series there were 35 successes. In 16 cases forceps were used. The greatest incidence of lack of control occurred in the period of transition between the dilatation of the cervix and the expulsion of the infant. No shortening of labor was observed. The duration of labor was not influenced by the number of calisthenics classes the patients attended. Four-fifths of the patients classified as emotionally very good obtained good results.

Tuberculosis.—Dr. João Bettega and co-workers (*Anais paranaenses de tuberculose e doencas torácicas*, vol. 2, June, 1957) reported on a series of 304 tuberculous patients subjected to 398 operations. Thoracoplasty resulted in cures in 62.5%, death in 14.5%, and positive sputum persistence in 23%. Many of the patients so treated did not benefit from modern bacteriostatic drugs. Late results from extrapleural pneumonolysis were: 73% cured, 11.6% died, and 15.4% with sputum still positive. Immediate results with extraperiosteal pneumonolysis were: 71.4% cured, 8.2% died, and 20.4% with sputum still positive. Pulmonary exeresis resulted in 1.2% with minimal, 30.4% with moderately advanced, and 68.4% with advanced lesions. Bronchial fistula was the main complication.

Hepatosplenic Schistosomiasis.—Prof. L. Bogliolo (*O Hospital*, vol. 52, Sept., 1957) stated that the commonest and most characteristic fibrosing hepatopathy of hepatosplenic intestinal schistosomiasis, namely, the Symmers type, was seen by him 24 times in 27 patients with hepatosplenic schistosomiasis in a total of 159 patients with schistosomiasis examined post mortem. The Symmers type is characterized by a chronic fibrosing granulomatous pylephlebitis and peripylephlebitis distributed systematically around the dichotomous portal branches without invasion of the lobules and without alteration of the architecture of the liver. Prof. Bogliolo presented the following theories about the pathogenesis of fibrosing hepatopathy in intestinal schistosomiasis of the Symmers type:

1. The hepatopathy of the Symmers type is due to the local action of dead schistosomes with the following succession of lesions: (*a*) embolism of the portal branches, (*b*) inflammation and necrosis of the surrounding tissues, and (*c*) formation of a fibrous scar. There are no objective studies to support this theory which seems to rest merely on hypothetical reasoning.

The items in these letters are contributed by regular correspondents in the various foreign countries.

2. The Symmers form develops exclusively in persons with unisexual infestation by male schistosomes, the fibrosis being determined by the products of disintegration. This theory, like the previous one, does not rest on a sound basis nor does it explain the macroscopic and microscopic findings.

3. The systematized periportal fibrosis of the Symmers type is due to the action of toxins arising predominantly from the schistosomes. Like those preceding, this theory has no anatomic or experimental basis, nor does it explain the typical systematized pylephlebitis and peripylephlebitis of the Symmers type.

4. The disintegration products of the schistosomes, their ova, their toxins and the affected tissues can act as allergens. This theory also is not based on objective facts. The fundamental error of this theory lies in wishing to presuppose a single mechanism for diseases whose causes and lesions are entirely different.

5. The hepatopathy of the Symmers type is due to cirrhogenous intestinal lesions or caused by schistosomal pigments. This theory is without any objective basis.

6. The hepatopathy of Symmers is caused predominantly by the action of ova on the connective tissue of the periportal sheath. Following the blood stream, the ova penetrate the two type of vessels springing from the portal branches: (*a*) the dichotomous branches that are distributed in a uniform manner throughout the liver, thus systematizing the process over the whole organ; and (*b*) the small nondichotomous branches that spring from all the dichotomous branches starting at the two chief branches, extending to the branches of the fourth order, and contributing to the formation of the periductal network. As a rule, these branchlets do not reach the lobules and do not contribute to the sinusoidal network. They terminate in the connective tissue which, like a sheath (Glisson's capsule), surrounds all the dichotomous branches of the intrahepatic portal tree. Thus the ova which penetrate fall into this perivascular connective tissue, die, and produce in it a granulomatous inflammation (peripylephlebitis) which extends to the portal wall (pylephlebitis). Reparative granulation tissue replaces the inflammatory tissue and is distributed systematically around the branches of the whole portal tree without, as a rule, going beyond Glisson's capsule. The newly formed vessels of this granulation tissue are derived exclusively from the nondichotomous portal branches of the periductal network. The newly formed connective tissue is derived from the periportal sheath. The apparent lack of proportion between the intensity of new formation of connective tissue and the number of ova is due to the faculty possessed by all helminthic ova of producing hyperplastic reactions and the fact that most cases of Symmers' type of hepatosplenic schistosomiasis are observed when the inflammation has already subsided and a large number of ova are already eliminated. However, by the use of proper techniques, a large number of ova or their residues can be discovered.

This theory is based on the following facts: (1) anatomically, the lesions found in the Symmers type are really a chronic granulomatous fibrosing pylephlebitis and peripylephlebitis; (2) there is a constant topographic relation among this distribution of the ova, inflammatory granulomas, granulation tissue, and vasculoconnective neoformation; the whole process occurs exclusively and electively in the perivascular connective sheath, limited by the invagination of Glisson's capsule and without any participation of the lobules and their connective tissue stroma; and (3) a reconstruction can be made of all the stages and phases, both of recent cases rich in ova and showing intense granulomatous inflammation and of old cases in which the inflammatory reaction has disappeared and the ova and their residues are scarce while the vasculoconnective neoformation is abundant.

INDIA

Typhoid in Children.—Taneja and Ghai (*Indian J. Pediat.* **24**:114 [Aug.] 1957) analyzed 205 cases of typhoid. The criteria for diagnosis were a positive blood or clot culture for Salmonella typhi or S. paratyphi A, a positive and rising agglutination titer in both flagellar and somatic antigens in a dilution of 1:250 or higher in noninoculated children, and a positive agglutination titer of 1:125 in both H and O antigens or 1:250 in either associated with suggestive clinical findings. The highest incidence was in the period between April and October, although positive blood cultures were detected in other months. Children of all ages were involved; 18 were under the age of three years in this series. The highest incidence was in those between 6 and 12 years of age. There were 134 boys and 71 girls. The onset was sudden in most cases. Continuous fever, abdominal distention, soft enlarged spleen, and bronchitic signs in the chest were common features. Bradycardia and rose spots were rare. Blood culture for S. typhi was frequently positive between the 7th and 40th day after the onset. Widal's reaction was variable and of no diagnostic significance.

The incidence of complications was low, many of them being due to prolonged starvation and emaciation rather than to the toxemia. The patients were kept at bed rest for a variable period but early ambulation was encouraged. They were given the regular hospital diet unless diarrhea was present. Unconscious children were fed through a nasal tube. Those with peripheral circulatory failure were given cortisone or corticotropin with encouraging results. Chloramphenicol was given orally to all but 17 patients. The average time for spontaneous recovery was 24.8 days, but with specific treatment it was 6.9 days; 38 patients did not respond to the drug when given for 10 days but showed improvement on its withdrawal. No cases of persistent vomiting due to the chloramphenicol given orally were observed. Relapses were seen in 15 children. Children with delirium or coma were given the drug by intragastric drip.

Pediatric Education in India.—The Medical Education Conference, in 1955, recommended that special departments of pediatrics be established in the medical colleges and that a period of not less than three months should be devoted to its study. Since 1947, much attention has been paid to improvement of child care programs and various state governments have undertaken comprehensive maternal and child health programs in the states. The government of India established a special course in Maternal and Child Health at the All-India Institute of Hygiene and Public Health, Calcutta. The Department of Maternal and Child Health was subsequently expanded in 1950 and the scope of training enlarged. The institution now trains 30 medical officers and 30 nurses in public health annually. According to the September issue of the *Indian Journal of Child Health*, various states have undertaken maternity and child welfare programs. About 1,200 pediatric beds have been provided in the pediatric units attached to the teaching hospitals. In some of the colleges maternity and child welfare centers have been associated with the pediatric units. In Nagpur Medical College, a unit for premature infants has also been established. The UNICEF and WHO have assisted in developing pediatric education by providing international personnel and essential equipment for these projects. Under the second five-year plan the government has provided $950,000 to assist states to develop pediatric centers attached to medical colleges to provide improved facilities for pediatric teaching of undergraduates. It is proposed to establish five pediatric teaching centers in the states.

Convulsions in Children.—M. V. Phadke (*Indian J. Child Health* 6:9 [Sept.] 1957) reported a series of 154 children with convulsions. Each child was subjected to a clinical examination, and samples of blood and spinal fluid were collected immediately after admission. The investigations included Wassermann and Kahn tests of the spinal fluid, blood smear for malarial parasites, leukocyte count, serum calcium and phosphorus estimations, funduscopy, blood pressure, blood urea determination, and sedimentation rate. An analysis of the results showed that the etiological factors that account for most convulsions in children are encephalitis, tuberculous meningitis, high fever, and hypocalcemic tetany. The first three years of the life of a child are the most hazardous as far as convulsions are concerned; about 69% of cases occur in this period. Almost 29% of all cases occur during the first year of life, 20% in the second year, and 18% in the third year. The incidence diminishes as age advances. Almost 75% of the cases of encephalitis occurred in the first 3 years; the same percentage was found for tuberculous meningitis; and 68% of the febrile convulsions occurred in this age period. All the cases of hypocalcemia and tetany were seen in the first year of life.

Bronchiectasis in Children.—S. S. Manchanda and co-workers (*Indian J. Child Health* 6:9 [Sept.] 1957) reviewed the etiological and clinical aspects of 50 selected cases of bronchiectasis in children. The diagnosis was confirmed by bronchography in 17 cases, while in the rest plain roentgenograms with typical history and clinical features were considered sufficient evidence for the diagnosis. Twenty-six of these children came from rural areas; 37 were boys and 13 were girls. The highest incidence was between the ages of 6 and 10 years, the youngest being 2. In 28, the onset occurred below the age of 5 years; in 19, between 6 and 10 years; and in 3, between 11 and 14 years. A history of some respiratory illness such as bronchitis, pneumonia, measles, or pertussis was obtained in almost every case. Most of the patients belonged to the poorer socioeconomic classes. Four had a history of chronic bronchitis in either parent, four of pulmonary tuberculosis in the family, and three of bronchonasal allergy. Cough was the universal complaint. In 46 patients it was productive and accompanied with expectoration in varying amounts. The minimum duration of cough was 6 or 7 months and the maximum, 11 years. Dyspnea was present in 30 patients. Hemoptysis was noticed in 10 patients, and it was never massive. Signs of malnutrition were evident in 15. Clubbing of nails was observed

in 13, and advanced pulmonary osteoarthropathy in 1. Chest deformities and abnormal spinal curvature were seen in four. There was evidence of emphysema in nine and chronic cor pulmonale in one. Moderate anemia was present in 18. The total leukocytic count was above 10,000 in 22. Sputum was negative for acid-fast bacilli in all. Cultures for pyogenic organisms were made in 23, of which 20 showed the normal respiratory flora, 1 showed Proteus vulgaris, and 2 showed Micrococcus pyogenes and Pseudomonas pyocyaneus. The roentgenographic findings were characteristic in all; 28 had cystic and 22 bronchiectatic lesions. The disease was unilateral in 34 and bilateral in 16. The lower lobes were chiefly involved, but there was no selective preponderance for either side.

Manufacture of Vitamins.—A number of schemes for the manufacture of vitamins have been approved by the government. Two of the schemes are for the manufacture of synthetic vitamin A from lemon-grass oil which is available in this country. Each of these schemes envisages an annual production of 10 million mega units of vitamin A. The production of shark liver oil, which is rich in vitamin A, has more than doubled in the last two years. The production in 1956 was 59,500 gallons compared with 27,158 gallons in 1954. Shark liver oil is produced by government factories in Bombay, Kozikode, and Trivandrum. A license has been granted to a firm under the Industries Act for the manufacture of vitamin B_{12}. It will have a capacity of 1.2 kg. a year. Licenses have been issued to two firms for the production of nicotinic acid and its amide. The total capacity will be about 15 tons a year.

UNITED KINGDOM

Influenza Vaccine.—Large amounts of Asian influenza vaccine are being prepared, but not enough for the entire population. The Ministry of Health decided not to use general vaccination against so mild a disease. The vaccine is being produced at the Wright-Fleming Institute of Microbiology, St. Mary's Hospital, London, and the Glaxo Laboratories. The initial output will be used for hospital and family physicians, nurses, and others particularly exposed to infection.

Salk Vaccine.—An editorial in the *British Medical Journal* (Sept. 21, 1957) comments on the about-face of the British Government in the matter of permitting the use of the Salk vaccine. The *Lancet* of the same date says that the risk from its use is negligible, once the vaccine has passed the prescribed safety tests. It is believed to protect about three people in four from paralytic poliomyelitis, but the duration of the protection is not known. About 100,000 doses of Salk vaccine have been given without any measurable ill-effects. The government has been beguiled into posing before the electorate as a kind of medical institution. Last year we had a Minister assuring the public that poliomyelitis vaccine was "absolutely safe," a statement that was not only inaccurate but inapplicable to any vaccine. Later another Minister, backed by some phoney statistics, declared that Britain's vaccine had been a success, when it was far too early to say. These were more than the injudicious slips of enthusiastic Ministers; they revealed politicians assuming all too easily a role they are not cast to play. Successive administrations are naturally concerned to promote public health, and, with the aid of the medical profession, create and operate statutory instruments to that end, but more than once they have shown signs of treating physicians as though they were rule-of-thumb technicians. The handling of the poliomyelitis vaccine has been symptomatic of this. It is an attitude that could quickly undermine public confidence in the medical profession and, moreover, do untold harm to the practice and development of medicine.

Doctors Want Cost of Living Adjustment.—Hospital and family physicians expect the Royal Commission on Doctors' and Dentists' Remuneration to take into account the rise in the cost of living, since the profession's claim for a 24% pay increase was submitted to the Ministry of Health in June, 1956. The British Medical Association has asked the Ministry to raise the interim awards made earlier this year. The commission's terms of reference require it to consider what should be the proper current levels of remuneration. It has also to consider arrangements for keeping remuneration under review. The association's evidence is a comprehensive document that covers all branches of the profession serving in the National Health Service.

Meeting of Medical Editors.—Medical editors from 24 countries met in London in September for the Third Congress of the International Union of the Medical Press. The Union was established at Brussels in 1953 and now has some 40 countries in its

membership. Medical journals have an important influence on the professional life of physicians, and their readers should benefit from the existence of an international forum for discussion of editorial practice and standards.

Prescribing Gin.—Gin can be prescribed under the National Health Service in certain circumstances because it makes a patient feel better. This was the decision of a Ministry of Health Appeal Board that upheld a physician's appeal against the Middlesex Executive Council. The council said that they were not bound to provide a patient with gin. The physician prescribed gin to make up a mixture of morphine and cocaine. The Appeal Board said they were satisfied that gin produced a sense of well-being that would not be given by ethyl alcohol and that it is the function of a physician to have regard for the mental state of his patient. They decided that this gin was, in the circumstances in which it was prescribed, a drug which the executive council were bound to provide.

Rheumatism Fight Aided.—Two fundamental discoveries in research into rheumatism were reported by Dr. W. S. C. Copeman, chairman of the Empire Rheumatism Council. Electron microscope studies showed that muscles consist of many varieties of fibers, not one type. Now it must be determined how many kinds there are and the effect on them of heat, cold, overwork, stress, and age. The second discovery was of a chondroitin sulfate complex, in the fluid surrounding muscles, that acts in much the same way that motor oil lubricates an engine. Research workers are trying to find the part this substance plays in keeping muscles in good condition.

No Free Operation.—A 54-year-old American was refused permission to land in England when he arrived at Tilbury from Spain. He is semiparalyzed and hoped to have a free operation in Great Britain. Immigration officials ruled he had not enough money to land.

New Drug Aids Alcoholics.—A new drug for the treatment of chronic alcoholics was tried in a hospital near London. First results suggest that it is dramatically effective in making alcohol unbearably unpleasant and has a more prolonged action than other available substances. It is called Temposil. One dose is effective for up to 24 hours and it appears to be free from the unpleasant side-effects (vomiting and lethargy) that makes alcoholics reluctant to take other antialcoholic drugs. Its discovery began with an occupational disease of workers in Canadian fertilizer factories. After a day of working with carbamide they found that a small glass of beer would make them ill and cause flushing of the face.

Surgery Helps Delinquents.—A Royal Society of Health meeting was told by Dr. D. A. Ogden that only one in eight youths from reform schools who had deformities of the nose corrected had been reconvicted after two years. Parental neglect often involves not only moral neglect but neglect of physical handicaps. Many youths have squints, crooked noses, nasal obstructions, limps, ugly scars, badly healed fractures, and other complaints. Such youths almost invariably either are obviously embarrassed by their disabilities or have covered their resentment with overcompensatory aggression. The group of youths who have undergone treatment for their disabilities are more successful by 33% in staying out of trouble on release than youths who have not received such attention.

Epidemic Myalgic Encephalomyelitis.—The medical staff of the Royal Free Hospital, London, has issued a report on the epidemic of myalgic encepholomyelitis that affected all the hospitals in the Royal Free Group. Within a period of four months, over 300 persons were affected, most of them members of the medical, nursing, auxiliary medical, and administrative staff—only 12 being patients; 200 were hospitalized, and the report is drawn up from data collected from these patients. When fully developed, the disease showed features of a generalized infection with involvement of the reticuloendothelial system and widespread involvement of the central nervous system. The earliest symptoms commonly were mild sore throat, malaise, and headache, frequently associated with disproportionate depression and emotional lability. Headache, frontal or occipital, was sometimes persistent and severe. Sometimes nausea, anorexia, and gastrointestinal disturbances occurred. The malaise and headache were out of proportion to the moderate fever. In most cases the major illness developed after these symptoms, with muscle pain, weakness, and involvement of the central nervous system. At first paresis was accompanied by hypotonia and severe pain on movement. The weakness was often in one half of the body, although later it became more extensive and fluctuating. It did not resemble the flaccidity due

to injury to a lower motor neuron with muscle wasting and loss of tendon reflexes, as seen in poliomyelitis. Some of the patients exhibited a peculiar jerking voluntary movement. Two of the characteristic features were the severe pain associated with muscular tenderness and the emotional instability of some of the patients. Some complained of hypersomnia, nightmares, panic states, uncontrollable weeping, and intense depression. Evidence of involvement of the central nervous system occurred in 74%, and lymph node enlargement, particularly of the posterior cervical group, was present in 73%.

The cranial nerves were affected in 46%, those concerned being mainly the ocular, acoustic, and facial nerves. Vertigo was an early symptom, sometimes persisting and occasionally becoming severe. Prolonged painful muscle spasms and cramps, bladder dysfunction, and cutaneous hyperesthesia or hyperpathia were common. Spontaneous pain was the commonest sensory manifestation. It was usually felt diffusely through a weak limb, and was associated with marked muscular tenderness. In the case of thoracic or abdominal pain, it was sometimes difficult to determine whether it was visceral or muscular. The clinical findings were those of a diffuse disorder of the nervous system, with signs of irritation and paralysis. The course was variable. Over 50% of the patients became symptom-free within a month; in 25% the symptoms lasted four to eight weeks; and in about 7% symptoms persisted for over three months. Four patients appear to have a permanent disability as a consequence of the disease. One of the most striking features was the psychiatric overlay. Many patients suffered from various psychological symptoms, chiefly depressive. Three required electroconvulsive treatment, and two were treated in a mental hospital.

No specific treatment was given. Trunk and limb pains, headache, muscle spasm, and vertigo were particularly resistant. Convalescence was slow. When attempts were made to hurry this, relapse occurred. Special laboratory investigations were unrevealing. Nothing abnormal was found in the spinal fluid. The epidemiology was baffling. The explosive nature of the infection suggested dissemination through a common vehicle, but investigation of water, milk, food, and sanitation gave negative results. The cause and mode of transmission remain unknown. The attack rate was greatest in the resident staff of the hospital and in women, who were affected four times as much as men. Nurses were involved more than any other group.

Radioactive Contamination.—The Atomic Energy Authority has suspended the distribution of milk in the neighborhood of the Windscale atomic reactor plant in Cumberland. As a result of the overheating of some uranium cartridges in the reactor, some radioactive iodine (I^{131}) escaped into the air and subsequently into fields in which cows were grazing. The affected area is 200 square miles, on which are 600 farms. The I^{131} escaped through the filters in the chimneys of the plant. Samples of milk contained six times the maximum permitted radioactivity, and as it was considered unfit for children, 25,000 gal. a day has been poured into neighboring rivers to find its way into the sea. Some of the plant employees have become contaminated. The Atomic Energy Authority stated that there was no danger to the cattle, water, or vegetables in the area. The ban on the consumption of milk produced in the contaminated area lasted about two weeks. This period was considered ample, as contamination of the milk should only last about eight days. Two reactors are now out of commission as a result of the incident.

Carbon Monoxide Poisoning.—In recent years there has been a progressive increase in the number of accidental deaths from carbon monoxide poisoning. Over 11% of deaths in the home are due to this cause, and 75% of these deaths occur in persons over 60 years old. The increase is not due to increased use of gas, as many new homes are now provided with electric fixtures throughout. Chalke and Dewhurst attributed many of these deaths to an impaired sense of smell in older persons (*Brit. M. J.* **2**:915, 1957). They devised an apparatus to detect the ability to smell coal gas in varying concentrations. It was found that about 30% of persons over the age of 65 could not recognize the smell of coal gas at a concentration below 50 parts per 10,000 of air, a lethal concentration if inhaled continuously. Of those older persons who can smell coal gas, 95% recognized 45 parts and 50% recognized 25 parts per 10,000 parts of air. On the other hand, 95% of persons under the age of 65 could recognize gas at a concentration of 45 parts, and 50% at a concentration of 8 to 10 parts per 10,000. Further tests showed that neither sex nor smoking had any effect on the threshold of recognition of coal gas. The large number of deaths from carbon monoxide poisoning in the elderly was attributed also to the leaving on of gas taps, or to gas leaks. It is hoped that an odorant that they can all detect will be found so that this may be added to coal gas to increase the threshold of recognition by smell. The use of odor as a danger signal for the accidental escape of unburnt gas is unreliable at present for older persons living alone. It is estimated that in

Great Britain one million people over the age of 60 live alone, and that many of these risk carbon monoxide poisoning.

Botulism in Labrador.—A fatal outbreak of botulism among a group of Eskimos in Labrador is described by Dr. J. Brocklehurst (*Brit. M. J.* 2:924, 1957). The party consisted of six men, two women, and some children, who went on a sealing expedition. Their food consisted mainly of utjak, which is prepared by placing seal flippers in a container and leaving it on a warm stove for several days. On this occasion the utjak was made in a gasoline can that had been previously used for storing decomposing sealskins and had not been cleaned. The food was kept in this flask at a temperature estimated to be between 20 and 40 C (68 and 104 F) for 10 days. After the party had consumed a meal of this utjak, one man vomited almost at once, and he was the only man to survive. A girl of 6 died two to three hours later. The second victim died four hours after the meal, and the remainder in the next three days. There were only two survivors, the man who vomited and a girl of 8. Two women who did not eat the utjak were unaffected. Those affected complained of difficulty in swallowing, regurgitation of fluids, abdominal pain and distention, vomiting, diarrhea, and headache. Samples of the food consumed and gastric contents of the victims showed the presence of Clostridium botulinum. This organism was later identified in a seal flipper obtained from the utjak, and type E toxin in a concentration of 1,000 MLD per gram of tissue was detected. The Eskimos had attributed the tragedy to the use of a metal gasoline can because the dish is traditionally made in a wooden cask and not eaten until the seal meat has putrified.

Urea as a Diuretic.—The diuretic properties of urea, which was used empirically before the introduction of the organic mercurials, has been reassessed by Papp and Smith (*Brit. M. J.* 2:906, 1957). The drug was given in doses of 15 Gm. dissolved in 60 cc. of water or grapefruit juice three times a day for periods of several weeks to seven years to 17 patients with prolonged right ventricular failure who were suffering from edema. Fourteen had chronic rheumatic heart disease, with hepatic cirrhosis and ascites; two had heart disease of coronary origin; and one was hypertensive. Treatment with urea was beneficial. In half the patients a negative fluid balance was changed to positive when urea alone was given. In patients in whom the balance remained negative, fluid retention was reduced. The effect of mercurial diuretics was potentiated, but even when they had failed urea still produced a diuresis. It also had the effect of preventing a rebound after mercurial diuretics were withdrawn.

Papp and Smith found that urea in the dosage given is harmless, but its use had to be discontinued in some patients because of unpalatability, or because of nausea and vomiting. They concluded that its administration may be the means of maintaining in a quiet occupation for several years a patient with grave valvular heart disease in whom relief is unattainable by any other form of medication. Patients with chronic congestive heart failure may benefit, at first by having months of activity free from edema, and later by the alleviation of the distressing edema and effusions that would complicate their last days of life. The average dose of urea given was 45 Gm. daily. Less than 30 Gm. may be insufficient to produce a diuresis, although it may potentiate the effect of mercurial diuretics and abolish water retention the day after the injection of the latter.

Arc Welders' Lung.—Arc welding is an important and expanding technique used in many branches of the engineering and shipbuilding industries. At the high temperature of the arc a gray-white vapor containing oxides of iron and other metals, nitrogen peroxide, and ozone is given off. The inhalation of these fumes, containing mainly iron oxide, gives rise to the condition known as arc welders' lung. It has always been thought that the radiologic changes occurring are benign and reversible and that those workers affected are asymptomatic. Mann and Lecutier, however, from examination of lung tissue after lobectomy, concluded that there was a distinct loss of lung elasticity in this condition, and this was confirmed by respiratory physiological investigations (*Brit. M. J.* 2:921, 1957). The maximal voluntary ventilation and timed vital capacity were 70% of expected values. After inhalation of the small particles of iron oxide, 1 μ in size, they were arrested in the peribronchial and perivascular lymphatics, and in the lymph nodes. The excised lung showed a marked degree of focal and lobular emphysema. Histological examination revealed the presence of pneumoconiotic bodies, similar to those seen in asbestosis and byssinosis, indicating a reaction of lung tissue to the iron oxide dust, which cannot for this reason be regarded as inert. Chemical and spectroscopic examination of the lung showed an iron content 100 times greater than normal. The prolonged inhalation of iron oxide fumes in an enclosed space with inadequate protection produced secondary emphysematous changes that might become extensive and permanent.

CORRESPONDENCE

INTRACUTANEOUS ADMINISTRATION OF ASIAN STRAIN INFLUENZA VACCINE

To the Editor:—Due to the shortage of the current Asian strain influenza vaccine, much interest has been raised as to the possibility of immunizing persons with 0.1 ml. of the vaccine injected intradermally rather than with the presently recommended dose of 1.0 ml. of the vaccine given subcutaneously. This thought has been raised by the intradermal use of other types of vaccine (*J.A.M.A.* **164:**1626 [Aug. 3] 1957) showing the development of antibodies but without the necessary proof of actual human protection in an epidemic. In the Correspondence section of THE JOURNAL (**165:**278 [Sept. 21] 1957), Dr. Louis Tuft implied that the intradermal injection of 0.1 ml. of influenza vaccine will confer protection against the disease. The basis for his recommendation is the production of antibodies as measured by the hemagglutination inhibition (HI) test after intradermal inoculation of the vaccine.

The production of HI antibodies does not necessarily indicate that human immunity against influenza will follow. Demonstration of the protection of the human subject by experimental or natural challenge with influenza virus must be carried out before one may accept the intradermal method of immunization as valid. Consequently, physicians must realize that, until such data are available, the satisfactory immunization of the human being is to be achieved in the adult only by the use of 1.0 ml. of influenza vaccine injected subcutaneously. Such is the stand of the U. S. Public Health Service (Communicable Disease Center Bulletin Report no. 18, Sept. 24, 1957) and the brochures accompanying influenza vaccine as supplied by the manufacturer.

Much erroneous information has been disseminated on the high reaction rates from influenza vaccine. This was true with the polyvalent influenza vaccine of the 1940's, which contained about 1,500 CCA units per milliliter of combined influenza virus (Sadusk, Bassett, and Meddaugh: *Am. J. Hyg.* **49:**148 [March] 1949) but the present monovalent vaccine containing 200 CCA units of influenza virus should have a significantly lower reaction rate since the frequency and severity of reaction is directly related to the virus content of the vaccine. That this is so has been adequately demonstrated (Sadusk and Nesche: *California Medicine,* Nov., to be published, 1957) for the currently available vaccine.

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PRELIMINARY FINDINGS ON VACCINATION AGAINST ASIAN INFLUENZA

To the Editor:—For the past nine weeks our group has been conducting extensive studies on the immunization of children, young and middle-aged adults, and older individuals against Asian influenza with use of monovalent vaccine obtained from three pharmaceutical houses. One lot of vaccine (A-1) contained 100 CCA units per milliliter. All the rest contained 200 CCA units. In all, more than 1,000 individuals were inoculated. These were divided into groups according to the following inoculation programs: (1) single subcutaneous injection of 1 ml. for adults and 0.5 ml. for children; (2) single intradermal injection of 0.1 ml.; (3) intradermal injection of 0.1 ml. into two sites; (4) primary inoculation of 1 ml. subcutaneously or 0.1 ml. intradermally followed by a second intradermal injection of 0.1 ml. one to six weeks later; (5) single injection of 0.1 ml. deliberately given subcutaneously; and (6) intradermal injection of 0.1 ml. of polyvalent vaccine lacking the Asian component.

All individuals were bled at the time of the initial injection and at specified intervals thereafter. Serologic tests have been completed on some of the individuals, others are now in progress, and still others will be carried out when the final bleedings on certain groups are accomplished.

The extent of systemic reactions (chills and fever) varied from lot to lot. The low potency lot produced almost no reactions. Lots from two manufacturers produced reactions in less than 5% in the intradermal group and in 10% in the subcutaneous group. Vaccine from a third manufacturer produced reactions in about 15% when given intradermally.

In terms of fourfold or greater antibody rise, as measured in the complement-fixation (CF) test, the low potency A-1 lot gave positive results in 78% when given by the subcutaneous route and in 45% by the intradermal. Two lots of vaccine with 200 CCA units yielded positive findings in 88 and 77% after subcutaneous inoculation and in 74 and 62% by the intradermal inoculations. Although the CF test brings out antigenic group reactions rather than specific strain reactions, it appears that these responses were at least in part elicited by the specific Asian influenza antigen components, for it was found that vaccine lacking Asian component produced CF antibody rise in only 11% of vaccinees.

We were especially interested in the effectiveness of second inoculations. The results shown in the table summarize the findings on young and middle-aged adults who were given a second inoculation

intradermally (20 CCA units) five weeks after the primary intradermal or subcutaneous injection. A large proportion of these individuals showed no antibody rise when measured by the CF test prior to reinoculation. Fourfold or greater complement-fixing antibody increases after booster inoculations were found in 35% of those initially inoculated intradermally and in 11% of individuals injected subcutaneously. The results were even more revealing when the hemagglutination inhibition (HI) tests were performed.

The boosting effect was not noted in children who were given the second inoculation 12 days after the first. Regardless of whether the second injection was given, 88% had a CF antibody rise after intradermal inoculation and 100% responded after subcutaneous inoculation of 0.5 ml. The HI antibody rise occurred

Findings in Individuals Given Booster Inoculations of Twenty CCA Units Five Weeks After Primary Injections

	Initial Injection, CCA Units			
	Intradermal		Subcutaneous	
No. Tested	10	20	100	200
Initial response, %	22	19	13	10
Significant*	41	68	70	100
Partial†	27	16	15	0
None	32	16	15	0
Booster response, %				
Significant	32	28	30	0
Partial	18	28	23	20
None	50	44	47	80
Net response, %				
Significant	68	79	92	100
Partial	27	16	8	0
None	5	5	0	0
Prebooster serums, %				
Titer of 1:80 or higher‡	18	26	54	90
Titer of at least 1:40‡	32	52	61	100
Postbooster serums, %				
Titer of 1:80 or higher	32	58	69	82
Titer of at least 1:40	68	89	100	100

* Percentage of individuals with fourfold or greater antibody rise.
† Percentage of individuals with twofold antibody rise.
‡ Arbitrarily selected reference points. The relationship of antibody titers obtained by different procedures and methods to actual immunity to Asian influenza virus has not yet been established.

in about 90% of both groups. A titer of 1:64 or higher was obtained in 62% of the intradermally inoculated and 44% of the subcutaneously inoculated children.

While definite conclusions and recommendations must await completion of this study, it appears that a second inoculation of 0.1 ml. of vaccine at an interval of five weeks improves the antibody response in individuals who have received a primary intradermal injection. (Additional findings show boosting effect also at three weeks.)

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INJECTION OF INFLUENZA VACCINE

To the Editor:—I have just seen Dr. Tuft's letter in The Journal, Sept. 21, 1957 (165:278) concerning the intracutaneous administration of Asian influenza vaccine. In this letter Dr. Tuft agrees with Dr. Hilleman that the 1.0-ml. subcutaneous method of immunization is somewhat more efficacious than the intracutaneous injection of 0.1 ml. (containing 16 units of Asian influenza virus vaccine). What surprises me is why these authorities limit themselves in the intracutaneous dosage to 0.1 ml. I have been using intracutaneous injections of 0.15 ml. for women and 0.2 ml. for men. The reactions have been negligible and the technique is made no more difficult by the increased dosage. The stronger (24 to 32 units) Asian influenza stimulus figures to be more potent antigenically and, accordingly, would elicit a better immunological response. We are also repeating the inoculation after a period of two to four weeks. I am among the patients who have received this immunization.

It is also to be noted that the manufacturers of the vaccine are planning to increase the potency of Asian influenza vaccine from 200 to 400 units per milliliter so that perhaps with this increased potency one could return to the 0.1-ml. dosage. However, I still believe that, when the more potent vaccine becomes available, I will still inject at least 0.15 ml. intracutaneously. Certainly the new vaccine will quite likely cause more reactions if given in 1.0-ml. dosage subcutaneously, but I doubt that this increased potency will cause any noticeable change if the intracutaneous method is employed.

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ELECTROSHOCK THERAPY AND PAIN

To the Editor:—I was interested to read Dr. Karl O. Von Hagen's article in the Oct. 19, 1957, issue of The Journal, page 773, in which he reported the relief of severe pain in eight patients by means of electroshock treatment. I can confirm the effectiveness of electroshock treatment in relieving chronic severe pain in some patients. Offhand seven cases come to mind. In two of them the severe abdominal pains of porphyria were relieved by electroshock treatment. Two other patients had chronic trigeminal neuralgic pains relieved by electroshock treatment. Three cases of headache were relieved by this treatment. All of these patients had been given extensive treatment, including psychotherapy, without benefit.

It has been my experience that patients suffering from chronic severe pain, even though there may be a large psychogenic element, are very difficult to

treat psychotherapeutically. The above patients came to electroshock treatment as a result of suicidal attempts because of their inability to withstand the pain any longer. One of the above patients had become addicted to narcotics because of the pain and after treatment was able to get along without narcotics. Occasionally it is necessary to give several courses of treatment where the pain recurs. Although it is impossible to tell ahead of time which patients with pain will respond to electroshock treatment, the experiences of Von Hagen would suggest that perhaps this therapeutic measure might be tried more often.

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LAW DEPARTMENT

MEDICOLEGAL ABSTRACTS

Food and Drug Acts: Homologous Serum Jaundice Following the Use of Pooled Blood Plasma.—This was a suit for damages for injuries caused by the administration of a quantity of blood plasma manufactured by the defendant pharmaceutical company. From a judgment for the plaintiff, the defendant appealed to the United States court of appeals, sixth circuit.

Having received a severe cut in his right thigh from a power saw, the plaintiff was taken in a state of shock to a hospital where his wife signed on his behalf a consent to any surgical or medical procedure the surgeon in charge of his case deemed necessary. Because of the plaintiff's condition, the resident surgeon administered a quantity of blood plasma before performing emergency surgery. The plaintiff made a normal recovery and was discharged from the hospital in about a week. About two months later, however, he became afflicted with jaundice and his condition was diagnosed as probable homologous serum hepatitis. The jury determined that the plaintiff's hepatitis was caused by the blood plasma, and the defendant did not dispute that finding on appeal.

The manufacture of plasma is regulated under the Virus, Serum and Toxin Act and the defendant was licensed to manufacture plasma, and did so, in conformity with the administrative standards promulgated thereunder. Blood plasma is a dried powder which by the addition of sterile water is quickly reconstituted into liquid blood plasma, which can then be administered as a substitute for whole blood. One of its major advantages is that it can be administered safely without the blood type of the recipient first being determined. The manufacturing process involves pooling the blood from a substantial number of donors and then processing the pooled blood so as to form the dried plasma. If the blood from a single donor contains the virus of serum hepatitis, there is a risk that a patient to whom the product is later administered may develop the disease. Unfortunately, this is a possibility that cannot be completely obviated. The presence of the virus cannot be determined by microscopic examination or by any other test known to medical science. It cannot be removed or destroyed by any known method which does not also destroy the utility of the plasma. Manufacturers are required to include in the labeling a warning calling the attention of physicians to the possibility that the patient to whom the product is administered may develop serum hepatitis, and such a warning was attached to the package of plasma administered to the plaintiff. The physician who administered the plasma said that he was aware of the possibility and referred to it as a "calculated risk."

The plaintiff's case was based on the contention that the defendant had violated the Tennessee Food, Drug and Cosmetic Act by delivering an adulterated drug, and that such violation amounted to negligence per se.

The food and drug act prohibits the sale or delivery of any drug that is "adulterated," and a drug is defined as being adulterated . . . "If it consists in whole or in part of any filthy, putrid, or decomposed substance." The plaintiff argued that the plasma in question was adulterated because the virus which it contained was a filthy substance. The courts of Tennessee have not had occasion to determine the meaning of this part of its statute. Since the state act was patterned upon the federal act, however, cases under that act were reviewed. The court of appeals said that the federal decision coming the closest to supporting the meaning which the plaintiff would ascribe to the term "filthy" is a case holding that bacteria, particularly the Bacillus typhosus, which had been absorbed by live oysters during their process of growth, rendered them filthy, "especially since the result of investigation has shown that filth or dirtiness is dangerous through the germs which it contains, and not solely because of offense to the senses." That decision is differentiable, however, said the court of appeals, for the reason that the bacillus there involved is microscopically detectable, and perhaps also because the typhoid bacillus was transmitted to the oysters in human sewage and other filth. The court, therefore, concluded that a virus which cannot be seen even with the most powerful microscope, which cannot be described, and the presence of which cannot be known at all except for its ultimate result is not a filthy substance within the intendment of the statute. Many drugs, said the court, contain substances of potential injury to health. This does not render them "filthy." Accordingly, the judgment of the trial court in favor of the plaintiff was reversed. *Merck and Company v. Kidd, 242 F (2d) 592 (1957).*

THE LEISURE CORNER

FUN AT THE PIANO

Many physicians love to play the piano. There are those who, having played the piano all their lives, look forward to improving their playing; there are those who have studied the piano in their youth, have given it up, and then decided once again to resume their interest in music; and finally, there are those who start to play the piano as adult beginners. Age is no opponent of the piano, as has been pointed out by Josef Hofmann, a universally renowned pianist: "The age of a student is immaterial. Provided there is a gift and intelligence, age need not stand in the way. If you are endowed with strong musical gifts in the abstract, you will achieve results superior to those attained by younger people with less talent."

More amateur musicians play the piano than any other instrument. The amateur does not have to go through the daily grind of enforced practice, and this makes the hobby an enjoyable experience. The piano poses interesting paradoxes. Unlike the violin, whose difficulties are apparent from the start, the piano is deceptively easy to play in an acceptable manner during the early stages of becoming acquainted with the instrument. Later on, however, the aspiring pianist becomes aware of such problems as muscular coordination and the musicointellectual content of a good composer's work. The truth is the piano is the friendliest of all musical instruments. It provides a familiar sight and sound in most cultured homes. In terms of mass communication, no radio or television station would dare operate without the piano for 24 hours.

Physicians generally make good pianists since they are primarily creatures of discipline and habit. These features supply the basic working prerequisites for playing the piano. Consequently, daily practice is a sound habit to acquire. Experienced teachers of the piano maintain that a daily practice session should be divided into three aspects—repertoire, technique, and sight reading. These will usually stimulate the amateur pianist who is bent on improving his mastery of the instrument.

Every musical composition mastered at the piano takes on a tie of close friendship, both during the time it is being learned and after it has been mastered. The closer one is drawn to a musical composition, the more enjoyment and satisfaction are to be expected and obtained. As mastery of the piano grows, the more likelihood there is of acquiring an expanding number of friends with similar tastes. Music is a powerful magnet that seldom fails to attract people who, by and large, are congenial, individual, and possessed of some creative ability.

Some years ago it was fashionable to discourage playing the piano by sight or ear since this supposedly was a distraction and even a harmful influence. At present, opposite views are held, for these practices are considered both pleasurable and informative. While playing the piano by sight or ear may tempt the student pianist away from more demanding musical tasks, if wisely administered in proper doses it will accomplish a change of tempo. As a rule, it is well for the budding pianist to postpone playing by ear and sight until the end of a formal practice session. Then there will be time enough for diversion and relaxation.

The ability to play by ear indicates a marked correlation between this aptitude and the ability to memorize. Invariably the novice pianist, who cannot play by ear, will memorize slowly or insecurely. Playing by ear contributes to that elusive quality of piano performance known as fluency. Playing by ear also leads to a grasp of harmony wherein notes are perceived in intelligible groups rather than one at a time. By referring to the piano as a mental concept that comes through the ear rather than across a printed script via the eye, the student pianist is able to take active steps to heighten his harmonic, melodic, and rhythmic acuity.

What, then, should be played by ear? The answer—anything and everything that appeals and that can be conjured up from memory of melodies. This most likely will include folk music, familiar themes extracted from often-heard classics, and jazz. Certain forms of jazz are today gaining recognition as an integral part of musical culture. In one way or another, playing jazz is a main ingredient of light modern music, foreign and domestic; hence its popularity. Actually, many jazz musicians are serious concert musicians.

There are certain advantages in playing before an audience, no matter how small. It is good to play before a group every time an opportunity presents itself. An audience changes the relation of the pianist to his instrument and to the composition that is being played. It is wonderful practice, especially since inadequacies may turn up where least expected. Indeed, working over a musical passage in which one is weak is much easier than tackling a new piece. Once the amateur pianist has his hobby well started, he will then find delightful moments recurring periodically, particularly on those occasions when a musical composition has been mastered and he is ready to commence another.

Numerous diversions surround the piano. "Gather-around-the-piano" songs are widely enjoyed today. Nobody has a better time than the pianist who is permitted by tradition to sing at the top of his voice—voice or no voice. Everybody likes to sing, whether hymns, classics, semiclassics or "boogie-woogie." Many amateur pianists enjoy accompanying solo singers or instrumentalists. Accom-

paniment trains them to play with an ear always alert to the requirements of the performing soloist. In such instances, the pianist becomes both leader and follower. Pianists frequently tend to seek out other kindred spirits for the purpose of playing piano duets. This leads to further developments in skill; one of the richest awards comes in the form of chamber music. Then again, there is the enjoyment associated with participation with the violin and the cello.

Familiarity with the piano leads some musicians to retrace the history of the piano. Occasionally, a few turn to the older relatives of the piano. Generations ago, in England, the spinet, or virginal, as it was called, was considered particularly suitable for young ladies. Later, the harpsichord, much more adequate musically than the spinet, became a favorite instrument in England, France, and Italy. Scarlatti, Handel, and a host of other composers wrote music specifically for this instrument. In Germany, on the other hand, long-lasting preference was directed to the clavichord. The clavichord was the favorite instrument of Bach, and it held the affection of German musicians long after the piano had replaced it in popular esteem. The chief difference between the three instruments—clavichord, harpsichord, and piano—lies in their individual action or method of tone production. In the clavichord, the strings are pressed by a small blade of brass; in the harpsichord, the strings are plucked by a plectrum operated by a "Jack" (the plectrum was once made of raven quills or leather); and finally, in the piano, the strings are struck by felt-covered hammers.

It is no exaggeration to say, in conclusion, that the longer one plays the piano, the greater is the appreciation and enthusiasm for the instrument. That is why so many physicians are drawn to it for enjoyment, fun, satisfaction, and relaxation.

MEDICAL FILM REVIEWS

Work of the Blood: 16 mm., color, sound, showing time 13 minutes. Collaborator: George E. Wakerlin, M.D., Chicago. Produced in 1957 by and procurable on loan or purchase from Encyclopaedia Britannica Films Inc., 1150 Wilmette Ave., Wilmette, Ill.

In this film, the functions and composition of the blood are described by photomicrography, animated drawings, and other photographic techniques. After a brief description of the work of the blood in circulating food elements and other materials to all body cells, in removing wastes, in helping to fight disease, and in helping to equalize heat distribution, the film illustrates the composition of the blood. Some of the elements in the plasma which are identified are salts, antibodies, fibrinogen, hormones, albumins and globulins, and wastes. A laboratory technician demonstrates how the number of erythrocytes in a patient's blood is determined, and a typical leukocyte is identified and described. The film explains that blood cells are produced mainly in the bone marrow. Animated diagrams identify the pulmonary and the systemic circulation. The work of the blood platelets in blood clotting is described, and an unusual, animated sequence shows the clotting and healing process of a wound. A method of blood typing is illustrated, and the four main blood groups are described. In addition, the film describes a test for the Rh factor. This film is technically accurate and well presented, with a good, understandable sound track; however, some of the vocabulary should be explained by the teacher before showing the film. The photography is excellent. The film is suitable for senior high school or college students in health and biology classes.

Congenital Atresia of the Esophagus: 16 mm., color, sound, showing time 23 minutes. Prepared by William L. Riker, M.D., Arthur DeBoer, M.D., and Willis J. Potts, M.D., Chicago. Produced in 1957 by Mervin W. LaRue, Inc., Chicago, and procurable on loan from American College of Surgeons, 40 E. Erie St., Chicago 11.

The management of the newborn infant with congenital atresia of the esophagus and tracheoesophageal fistula represents an interesting, almost classic example of medical and surgical achievement. In this film, which depicts the signs and symptoms of the condition, the diagnostic procedures, the operation itself, and the postoperative care, the authors have shown the present-day methods of recognizing and dealing with this lesion and with its real and potential complications. Statistical data are well shown in animation; the narration is excellent in text and delivery; and the all-important postoperative care is clearly illustrated. The major part of the film deals with the surgical correction of the anomaly. Each step is clearly illustrated. The operative field is always well oriented and exposed, well illuminated, and adequately described. Considering the small size of the thorax of the newborn infant and the technical problems, not only of the surgery but of the photography, in an infant of less than 6 lb. in weight, this is an exceptionally good record and teaching film. It is directed toward the medical student as well as toward the specialist—be he pediatrician or thoracic surgeon; it also reaches the general practitioner and obstetrician, who are often the first to encounter the problem.

ILLUSTRATED FILM REVIEWS

Illustrated reviews of current films, a regular feature in THE JOURNAL, *consist of an introduction by the author followed by a pictorial digest of actual frame enlargements selected as key points of the film.*

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Motion Pictures and Medical Television, Council on Scientific Assembly.

PRINCIPLES OF FRACTURE REDUCTION

William A. Larmon, M.D., Chicago

This is the introductory film in a series of 10 dealing with fractures of the long bones. It is concerned not so much with techniques of management as with the principles underlying the techniques. These principles are dramatized by a situation in an isolated farmhouse where a doctor is confronted with the necessity of reducing various fractures without the aid of the many gadgets available in hospitals. The written review of this film appeared on page 1308 of the Dec. 5, 1953, issue of THE JOURNAL.

Fig. 1.—Principles of fracture reduction have changed little over the centuries; however, they tend to become obscured by the profusion of devices available today.

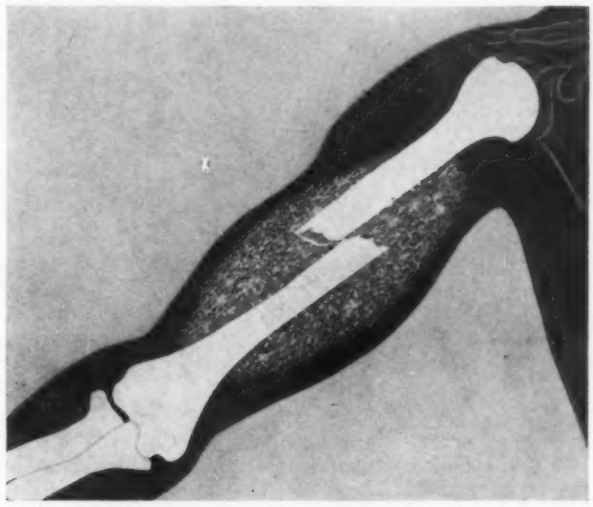

Fig. 2.—Reduce the fracture early. Each hour there is progressive diffusion of blood and induration of soft parts. Swelling causes the fascia to bulge, resulting in actual shortening.

Fig. 3.—Use slow, steady, nonvibrating traction. Gravity is frequently used: the force is exerted on the operator and thence through a shoulder sling to the fractured limb.

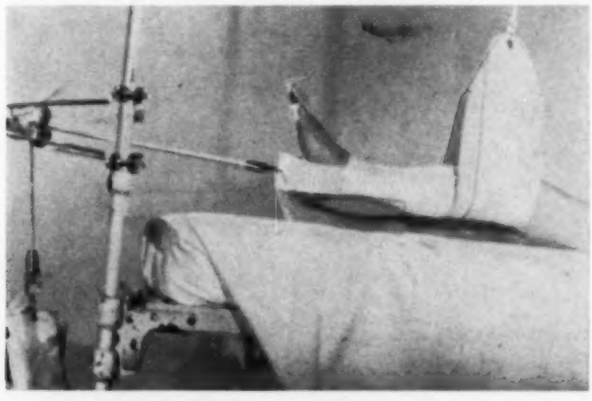

Fig. 4.—Gravity is also used by means of weights, pulleys, screws, windlass, and levers. The important point is that each exerts a force that is slow, steady, and nonvibrating.

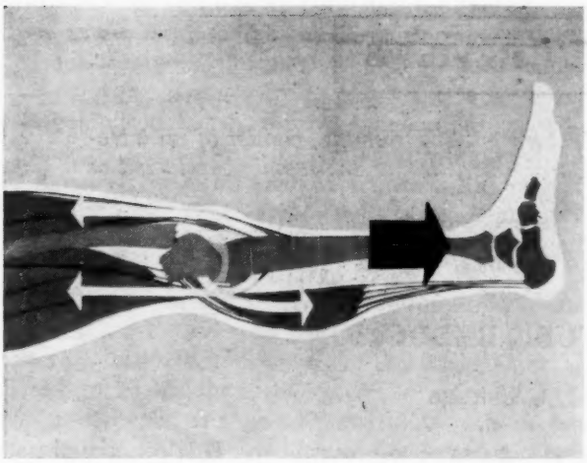

Fig. 5.—Neurtalize the displacing pull of muscles. The characteristic displacement caused by the pull of muscles can be overcome in two ways. First, traction may be applied in a direction to neutralize the opposing force.

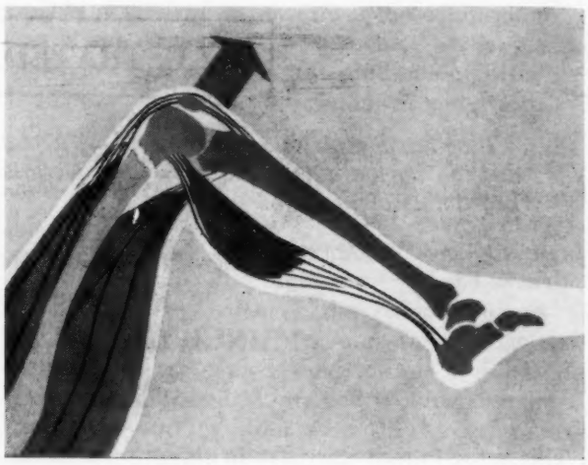

Fig. 6.—Second, the pull of muscles may be partly neutralized by putting the limb in such a position that the muscle does not exert so great a pull. In practice, both traction and placement are used where possible.

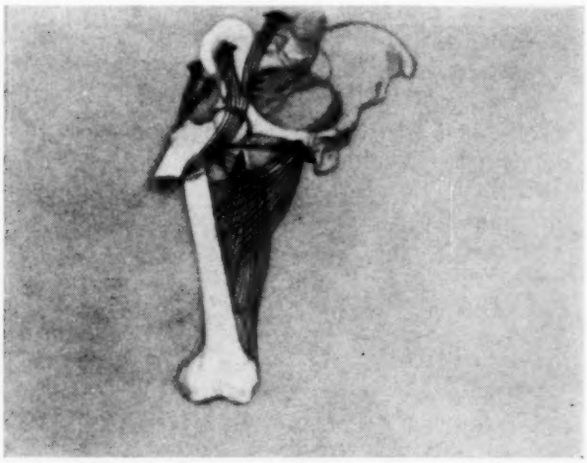

Fig. 7.—Align the fragment that can be controlled with the one that cannot. The distal fragment to be aligned must be pulled down, flexed, abducted, and externally rotated.

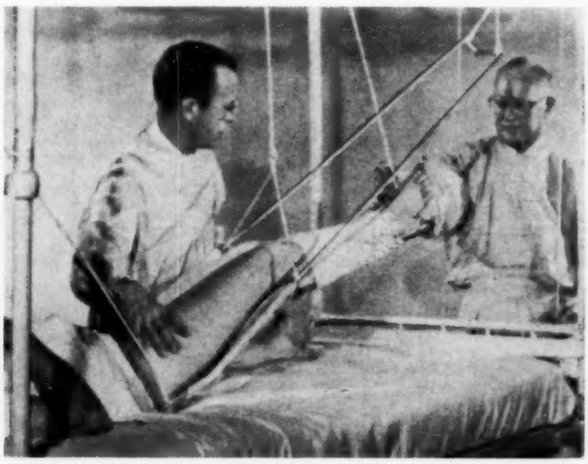

Fig. 8.—After reduction the principle applies as well to maintenance of reduction. Traction must hold the fragment that can be controlled in proper alignment and rotation.

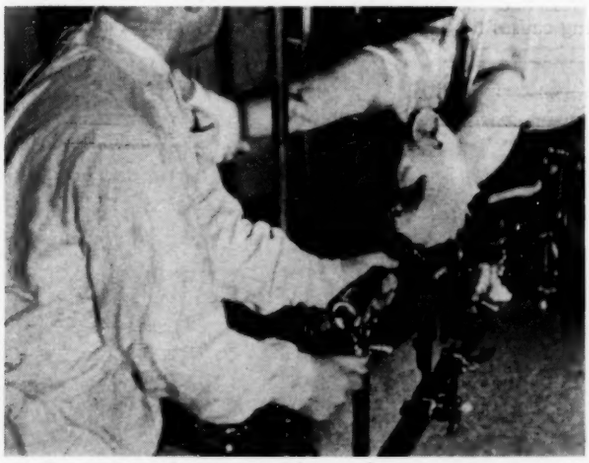

Fig. 9.—Traction requires countertraction. Without countertraction during reduction the patient is dragged to a point where the traction is no longer effective.

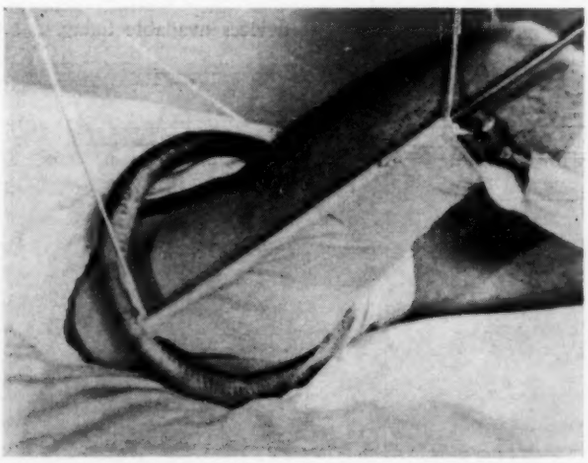

Fig. 10.—Countertraction is needed in maintenance of reduction as well as in reduction. Often the patient must be fixed in bed by some form of apparatus.

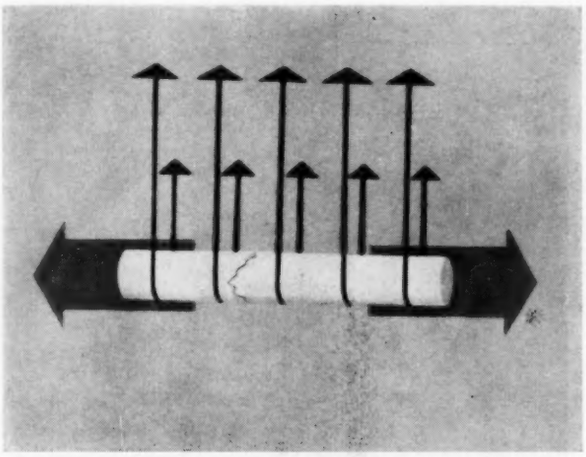

Fig. 11.—Maintain reduction by suspension, with traction and countertraction. A straight line of pull should be maintained even when the patient moves.

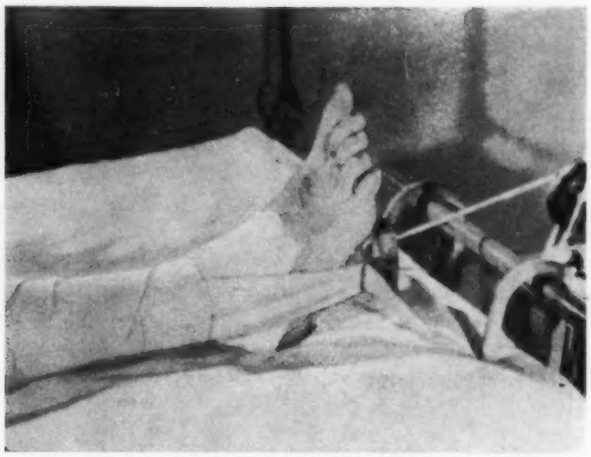

Fig. 12.—The most common of the various methods of fixing the traction apparatus to a suspended limb is skin traction.

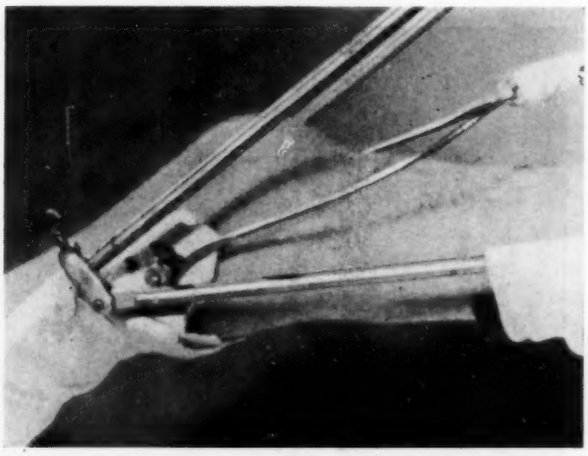

Fig. 13.—Skeletal traction is also frequently used: a Steinmann pin in cancellous bone, Kirschner wire more commonly in cortical bone.

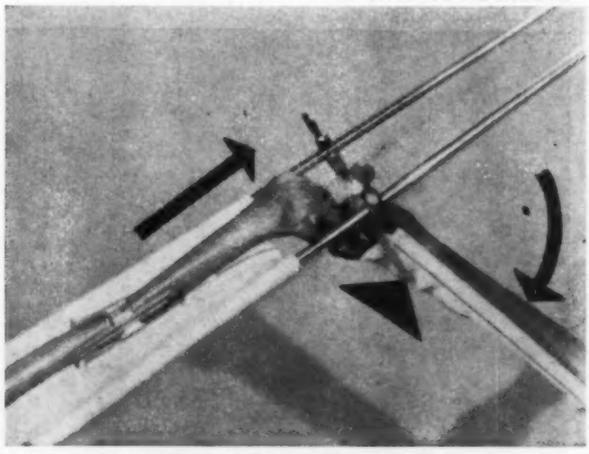

Fig. 14.—A third method of maintaining traction is through the ligaments and joints. The canvas below the joint provides a fulcrum. When the leg is flexed, the tibia acts as a lever exerting traction on the femur.

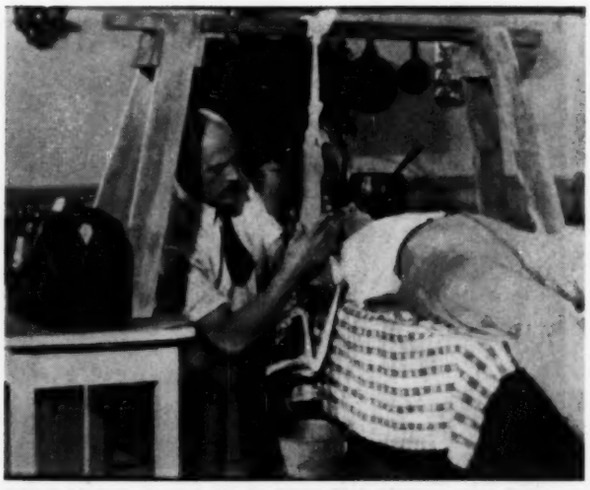

Fig. 15.—These fundamentals can be applied in isolated situations. In a forearm fracture a sawhorse and bucket of water provide nonvibrating traction and countertraction.

Fig. 16.—The suspension allows freedom to align the distal fragment with the proximal and to apply a cast without help.

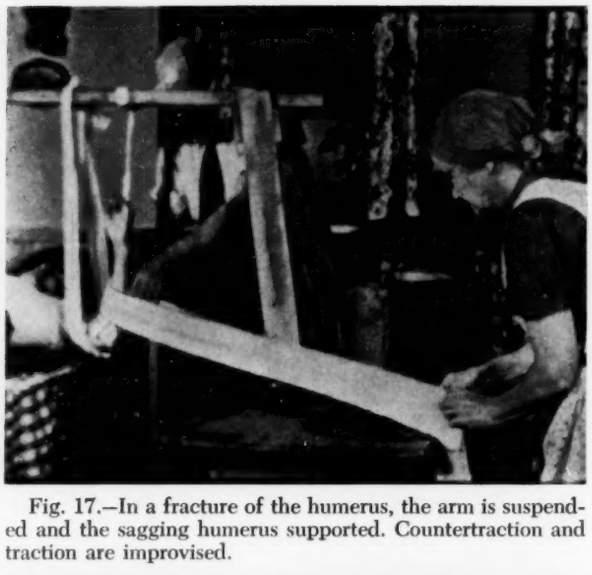

Fig. 17.—In a fracture of the humerus, the arm is suspended and the sagging humerus supported. Countertraction and traction are improvised.

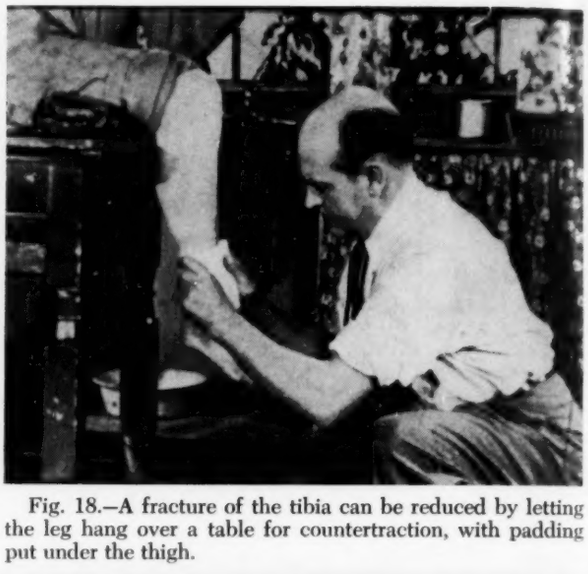

Fig. 18.—A fracture of the tibia can be reduced by letting the leg hang over a table for countertraction, with padding put under the thigh.

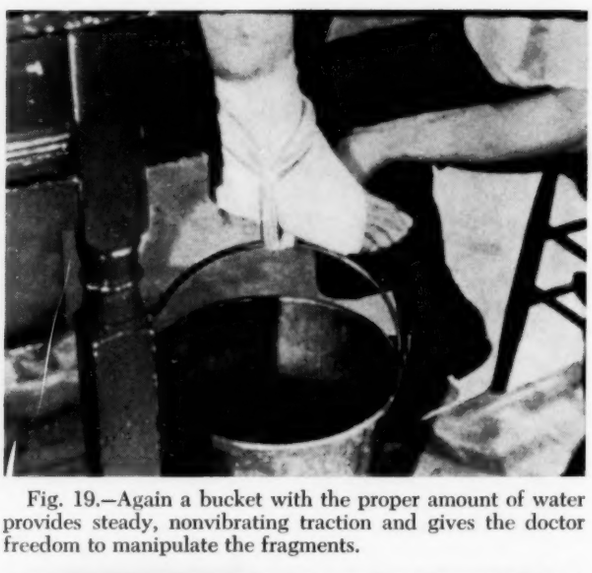

Fig. 19.—Again a bucket with the proper amount of water provides steady, nonvibrating traction and gives the doctor freedom to manipulate the fragments.

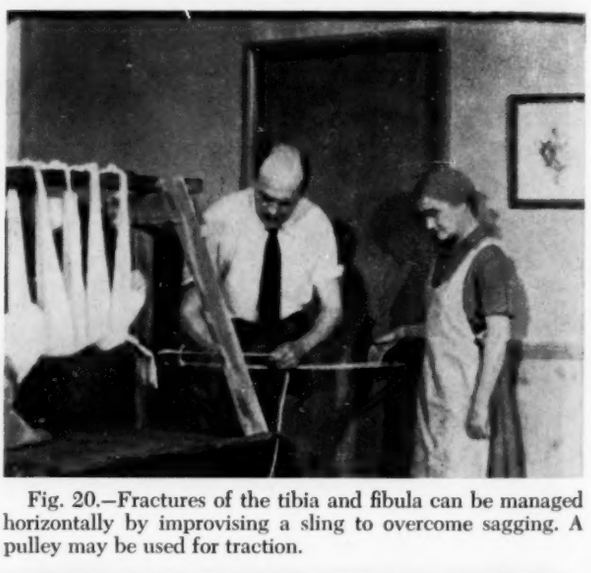

Fig. 20.—Fractures of the tibia and fibula can be managed horizontally by improvising a sling to overcome sagging. A pulley may be used for traction.

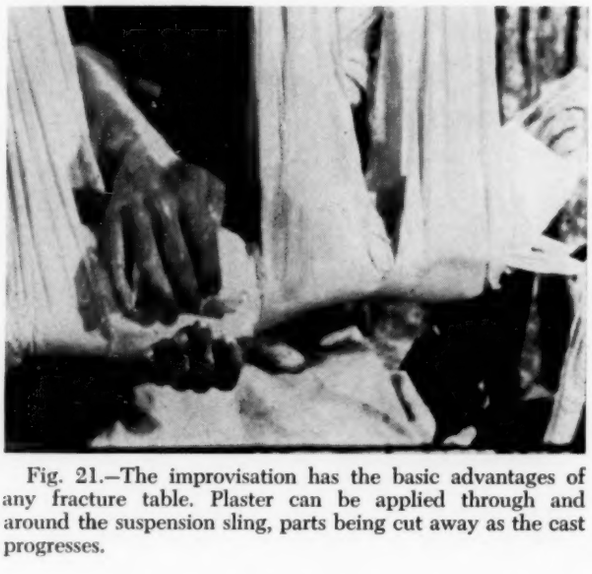

Fig. 21.—The improvisation has the basic advantages of any fracture table. Plaster can be applied through and around the suspension sling, parts being cut away as the cast progresses.

Fig. 22.—Though a fracture of the femur may be reduced by improvising the pulleys or weights, these are never as good as a Thomas splint in allowing the application of basic principles to both reduction and maintenance.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Studies in Hodgkin's Syndrome: XII. Hereditary and Epidemiologic Aspects. J. W. DeVore and C. A. Doan. Ann. Int. Med. 47:300-316 (Aug.) 1957 [Lancaster, Pa.].

A careful study of the charts of approximately 400 patients treated for Hodgkin's disease at the Ohio State University Health Center and of approximately 40 patients seen at the University of Oklahoma Medical Center revealed 15 families in which multiple cases of Hodgkin's disease or forms of lymphomas developed in blood relatives with or without direct contact, and in some instances with an interval of some years between. There were 6 additional families with presumptive multiple intrafamilial incidence. Although a husband and wife developed Hodgkin's disease at the same time, the clinical evidence for the disease being directly transmissible is slight and the experimental evidence in the literature inconclusive. The epidemiology of the disease, with the etiology still unknown, is difficult of determination, due to the probable multiplicity of healthy "carriers" for every active case in which an infectious agent is involved. The statistical data do not support either dominant or recessive gene factors as influencing incidence and expressivity of Hodgkin's disease. The evidence does suggest that in some families the reticuloendothelial system may be more susceptible than in others to as yet undetermined and unidentified environmental factors which may precipitate the development of lymphomas.

Chemical Determination of Urinary Catecholamines: An Aid in the Differential Diagnosis of Essential Hypertension and Pheochromocytoma. R. J. Henry and C. Sobel. A. M. A. Arch. Int. Med. 100: 196-200 (Aug.) 1957 [Chicago].

The authors studied the urinary excretion of catecholamines (epinephrine and arterenol) in 66 patients with hypertension whose diagnoses included essential hypertension, anxiety state, malignant hypertension, pheochromocytoma, and miscellaneous. Six established cases of pheochromocytoma were encountered. Most patients with pheochromocytoma manifest only a persistent hypertension and are difficult to differentiate from those with essential hypertension. Apparently 1 out of every 200 cases of hypertension involves a pheochromocytoma. It thus becomes important to have a highly specific method for the diagnosis of the latter condition. The most specific test for pheochromocytoma is the determination of urinary catecholamines. Catecholamines can be determined by bioassay and by chemical methods, but the latter are simpler and less costly. The authors have obtained what they consider to be an improved technique of chemical determination of catecholamines. It includes determination of the sum rather than individual quantities of the epinephrine and arterenol, a procedure believed sufficient for diagnostic purposes; increased accuracy by running an internal standard with each urine, since there appear to be variable amounts of "quenching" substances present in urine eluates; replacement of the manganese dioxide of Lund by the ferricyanide reagent of Ehrlén for greater speed and convenience; and simplification of the pH adjustment of column eluates by use of a standardized buffer. The method can be performed by any qualified technician under the supervision of a clinical chemist.

Diabetes Mellitus Complicated by Bacteremia Caused by Gram-Negative Bacilli. W. J. Martin, J. A. Spittel, W. M. McConahey and W. A. Bennett. A. M. A. Arch. Int. Med. 100:214-220 (Aug.) 1957 [Chicago].

Infection of the blood stream is of significant occurrence in patients with diabetes mellitus. Of 137 patients with bacteremia caused by gram-negative bacilli studied at the Mayo Clinic, 14 had diabetes. The coli-aerogenes group of organisms accounted for 12 of the 14 infections of the blood stream, and Proteus organisms for the other 2. An operation on or a manipulation of the urinary tract preceded bacteremia in 7 of the 14 patients. The urinary tract was the apparent portal of entry of infection in 13 of the 14 patients. Recovery from the bacteremia occurred in 7 patients receiving both a streptomycin compound (streptomycin or dihydrostreptomycin or equal parts of each) and one of the tetracycline group of antibiotics (chlortetracycline, oxytetracycline, or tetracycline). One of these

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patients died later of pulmonary embolism. Recovery also took place in 3 patients receiving only one of the tetracyclines and in one patient receiving only a streptomycin compound. One patient who received what would be considered inadequate therapy also recovered. Death occurred in 2 of the 14 patients during treatment of the bacteremia. One of these patients received only chlortetracycline, and the other received both streptomycin and polymyxin B. Both of them had serious renal disease, which probably made recovery impossible. Complication of bacteremia in diabetic patients is possible when infections of the urinary tract exist. The authors advise the prophylactic administration of a streptomycin compound together with one of the tetracyclines to diabetic patients before and after an operation on or manipulation of the urinary tract.

On Sjögren's Disease. L. Szanto, K. Farkas and E. Gyulai. Rheumatism **13**:60-63 (July) 1957 [London].

In an earlier report on Felty's syndrome and Still's disease, the authors had suggested that both these conditions, as well as Reiter's syndrome and Sjögren's disease, have a common, rheumatic etiology. The difference in symptoms can be explained on grounds of the difference in organic manifestations, but the disease is localized essentially in the mesenchyma. The authors present the histories of 2 women, aged 68 and 56, with Sjögren's disease. Sjögren's disease is characterized by a decrease or total absence of lacrimal and salivary secretion. Dryness of the skin and gastrointestinal disturbances may also occur. Sjögren found arthritis in 80% of his patients. One of the 2 women presented in this report died, and autopsy was performed. The histological changes confirmed the view that Sjögren's disease develops on the basis of rheumatic allergic mesenchymal lesions. Perivascular changes characteristic of rheumatic disease and also the marked glandular atrophy were the most remarkable findings. The latter explains the peculiarities of the clinical picture. The presence of perineural and intraneural infiltration was also of interest. Similar observations have been reported in cases of rheumatoid arthritis. This, too, seems to suggest that Sjögren's disease is a clinically well defined entity in the group of rheumatic diseases.

The Murray Valley Rash. J. G. Wilson. M. J. Australia **2**:120-122 (July 27) 1957 [Sydney].

In April of 1956, there occurred at Renmark, a town in South Australia, an epidemic of an illness whose chief feature was a rash. Forty-five cases have been recorded. Since the illness did not incapacitate most of the patients, many did not report. The rash was a maculopapular eruption; in some patients the lesion was discrete and red and pinpoint in size, while in others the coalescence of the lesions gave the rash a more blotchy, often a morbilliform aspect. The rash reached its peak in a few hours. Usually it lasted for 2 to 3 days. In more severe cases it lasted longer. In one-third of the patients there was no irritability. The lesions often first occurred on the wrists and ankles. The rash became generalized in the more severe cases and was most intense on the face and neck. More than one-third of the patients in the series complained of joint pains. There was a lack of general symptoms. Had it not been for the epidemic, an isolated case might have been diagnosed as rubella. The incubation period was probably 14 days. The proportion of male to female patients was 2 to 1. No causative organism has been isolated.

The rainfall in 1956 had been in excess of the usual amount in the area. Other epidemics of a similar nature also occurred in wet seasons in Australia. The chief differentiating feature was the range, extent, and severity of the polyarthritis, which was far greater in previous epidemics than in this one. The illness is probably a viral infection, being spread by mosquitoes, and possibly has its origin in birds migrating to the fertile wet land of the Murray basin in the wet season.

Differentiation of Macrocytic Anemias and Diagnosis of Pernicious Anemia and Sprue in Remission by Accelerated Measurement of Hepatic Uptake of Radioactive Co^{60} B_{12}. G. B. J. Glass and L. J. Boyd. Ann. Int. Med. **47**:274-292 (Aug.) 1957 [Lancaster, Pa.].

The determination of the presence or absence of Castle's intrinsic factor in the stomach has diagnostic significance, since its secretion is abolished in pernicious anemia but is usually well preserved in all other macrocytic anemias. Until recently the tests for the presence or absence of intrinsic factor in the stomach required a difficult assay of intrinsic factor activity by repeated counts of reticulocytes and red cells after administration of the tested gastric juice to a patient with pernicious anemia in relapse. With the advent of vitamin B_{12} labeled with the radioactive form of cobalt, Co^{60}, or, recently with Co^{58} or Co^{57}, this task has become much easier. The authors present a simplified and accelerated modification of the measurement of the hepatic uptake of radioactive B_{12}. They show that the measurement of hepatic uptake of vitamin B_{12} with Co^{60} aids in (1) differentiation of various macrocytic anemias; (2) the detection or ruling out of pernicious anemias, both in relapse and in remission; (3) the diagnosis of sprue, especially in the oligosymptomatic or asymptomatic stage of disease; and (4) the differentiation of simple anacidity refractory to histamine from that due to the gastric atrophy of pernicious anemia in the nonanemic or preanemic stage.

The hepatic uptake is normal in anemias due to blood loss, hemolytic anemias, and nutritional macrocytic anemias due to dietary deficiency of folic acid or B_{12}. On the other hand, the hepatic uptake is either entirely abolished or found only in traces in patients with pernicious anemia, in relapse, remission, or in the preanemic stage, but it can then be corrected by the addition of intrinsic factor. In sprue, and in some cases of regional enteritis or intestinal shunt, the hepatic uptake is also zero or appears only in traces, but it cannot be corrected by the addition of intrinsic factor. Measurement of the hepatic uptake in its accelerated form allows one to rule out pernicious anemia in 48 hours and to make a diagnosis of pernicious anemia or sprue within 4 days, without regard to the previous treatment or to the stage of the disease. In time requirement it matches the urinary flushing test and is not subject to errors due to the inadvertent discarding of a urinary specimen by the patient. The test can be performed in any clinical isotope laboratory which has the ordinary equipment for the measurement of the uptake of radioactive iodine by the thyroid, and the actual single measurement takes only 30 minutes.

Some Epidemiological and Laboratory Observations on an Epidemic Rash and Polyarthritis Occurring in the Upper Murray Region of South Australia. C. O. Fuller and P. Warner. M. J. Australia **2**:117-120 (July 27) 1957 [Sydney].

In April and May of 1956, a mild epidemic disease appeared in towns along the Murray River of South Australia. Sixteen persons were interviewed at various stages of the disease. The clinical features were a maculopapular rash, not usually itchy, of short duration, and polyarthritis. There was absence of fever and general symptoms. These symptoms resembled the descriptions by Halliday and Horan of 3 epidemics of polyarthritis, which occurred during the war in troops in northern Australia during the wet season. These reports gave greater prominence to the occurrence of polyarthritis, whereas in the present epidemic the rash was the most notable feature. The rash was not widely distributed over the body, but no part of the skin was exempt. The joint pains persisted longer than the rash. The disease seemed uncommon among children. There was no evidence of person-to-person infection. Specimens of blood clots from 14 patients were inoculated into guinea pigs, mice, and yolk sacs of embryonated eggs (6 days). The results failed to identify an infectious agent. The authors assume that this epidemic may have been initiated by the unusual concentration of susceptible people attending a regatta on Lake Bonney during Easter, 1956. It is unlikely that the infectious agent is normally carried by mosquitoes. The suddenness of the outbreak, followed by its more gradual disappearance, suggests that the infectious agent is not normally present in the region or that if it is, its presence was revealed by a concentration of large numbers of susceptible human beings. It may also be significant that there had been a particularly rainy season in the area and that there were more mosquitoes than usual. The authors conclude that the preceding 4 epidemics were caused by the same or closely related infectious agent spread by mosquitoes from an animal reservoir. If the disease was caused by a virus carried by insects, then the incubation period was probably between 3 and 15 days.

Isolation of Brucella Abortus by Percutaneous Liver Biopsy. F. B. Cohen, B. Robins and W. Lipstein. New England J. Med. **257**:228-230 (Aug. 1) 1957 [Boston].

The history of a 26-year-old man is presented who was admitted complaining of fever, night sweats, anorexia, malaise, and a productive cough of 2 weeks' duration. Agglutinins for Brucella abortus were present in the serum, with a titer rising to 1:6,400. Br. abortus was cultured from half the specimen obtained in the second percutaneous liver biopsy (the first performed on the 6th, the second on the 18th hospital day). Serial histological changes in the liver before, during, and after antibiotic therapy are described. No signs or symptoms referable to liver disease and no laboratory evidence of hepatic dysfunction were present in the patient. The authors conclude that, in suspected cases of brucellosis with negative blood cultures, percutaneous needle biopsy of the liver, with culture of a portion of the specimen and histological study of the remainder, constitutes a valuable addition to the diagnostic armamentarium.

Value and Significance of the Determination of C-Reactive Protein and Glutamine Oxalacetic Transaminase in Patients with Myocardial Infarction. U. Carcassi and F. Pitzus. Minerva med. **48**:2449-2458 (July 21) 1957 (In Italian) [Turin, Italy].

Glutamine oxalacetic aminopherase (transaminase) and C-reactive protein were studied in 25 patients with myocardial infarction. A marked increase in the values of the transaminase was found in 14 patients with recent myocardial infarction, and C-reactive protein usually appeared 12 hours after the onset of the infarction. The values of the transaminase became normal within 14 to 15 days, but the C-reactive protein still remained. The values of the transaminase were slightly elevated in 1 of the 8 patients with subacute or latent infarction; C-reactive protein was present in all 8 patients. Transaminase values were normal and C-reactive protein was absent in 3 patients with coronary insufficiency. The authors believe that transaminase

and C-reactive protein tests are of great help in diagnosing myocardial infarction when more common tests fail to give definite indications.

SURGERY

The Post-commissurotomy Syndrome: Clinical Study and Laboratory Tests. S. D. Volta and C. Picone. Minerva med. **48**:2287-2291 (July 4) 1957 (In Italian) [Turin, Italy].

One hundred fifty patients who had been subjected to mitral commissurotomy were followed for a period of from 2 months to 4 years. Thirty-five patients did not complain of rheumatic symptoms before the operation. A true postoperative rheumatic relapse was observed in 2 patients and a probable rheumatic relapse in 2 other patients. Relapse occurred 2 to 6 months after the operation and was checked with hormonal therapy. Sixteen patients presented a postoperative syndrome characterized by a sudden and acute onset, high and persistent fever, pain in the thorax or in the left shoulder, and pleural effusion. No clear signs of pericarditis were observed.

The authors do not believe that the rheumatic relapse was the cause of the syndrome. Instead, they attach great importance to allergic factors dependent on antistreptococcic hyperergy and on the particular "immunological polarization" of the patients. It seems conceivable that aspecific stimuli, combined with the depressed hypophysial-adrenocortical function resulting from the surgical shock, may cause an aspecific streptococcic reactivity.

Clinical Appraisal Of Percutaneous Splenoportography. M. S. DeWeese, M. M. Figley, W. J. Fry and others. A. M. A. Arch. Surg. **75**:423-435 (Sept.) 1957 [Chicago].

The technique employed in percutaneous splenoportography is similar to that used by Abeatici, Dreyer, and Sotgiu, in which an intercostal approach is employed in the administration of 70% sodium acetrizoate (sodium Urokon) as a contrast medium. An automatic filming device permitting serial exposures at the rate of 1.3 per second has been utilized in three-fourths of these examinations. While the latter modification is not essential to the success of the procedure, many satisfactory examinations have been accomplished by rapid manual changing of the cassettes, and it is a helpful technical refinement. One or more successful examinations have been accomplished in 103 of the 120 patients (85.6%). Multiple examinations have been successful in some of these patients, while in others reexamination after an initial failure was successful. A total of 134 examinations have been attempted, of which 113 (84.3%) have been successful, with the technical quality good in 70.1%, the examination itself of substandard quality in 14.2%, and the remainder (15.7%) complete failures. The cause of failure in 15 attempts was either the inability to position the needle correctly within the spleen or retrograde extravasation of contrast material along the needle tract after it had entered the spleen rather than passing into the portal circulation. No deaths were attributable to this procedure, and in no patient has the need arisen to perform emergency splenectomy because of hemorrhage, although one patient with unrecognized thrombocytopenia did develop evidence of intra-abdominal hemorrhage and required 1,500 cc. of blood to combat shock.

In portal hypertension from any cause, there is a reverse flow of varying degree of contrast material into the tributaries and collaterals of the portal circulation. Cirrhosis of the liver is suspected on the basis of abnormalities in the size of the liver, crowding or tortuosity of the larger venous branches within the liver, or attenuation of the peripheral branches. The diagnosis of portal hypertension of intrahepatic origin is made on the basis of the visualization of collateral channels, patency of the splenic and portal veins, and the above radiologic indications of cirrhosis. Extrahepatic portal obstruction, associated with cavernomatous transformation of the portal vein, is diagnosed on the basis of tortuous channels in the region of the hepatoduodenal ligament. Portal hypertension due to hepatic vein obstruction (Chiari-Budd syndrome) is suspected on the findings of a patent portal vein, distended collateral channels, and normal intrahepatic branching of the portal vein in the presence of normal liver function. Intrahepatic neoplasms produce blunting of the larger portal branches within the liver, or mottled densities in the hepatogram. Extrahepatic neoplasms are characterized by filling defects of the portal or splenic veins or complete block with filling of collateral channels distal to the point of obstruction. Complete obstruction of the splenic vein by neoplasms in the tail of the pancreas may cause nontransit of the contrast medium from the spleen and must be evaluated carefully.

Percutaneous splenoportography confirmed a diagnosis of portal hypertension of intrahepatic origin in all of the 12 patients presenting clinical evidence of cirrhosis and esophageal varices proved by esophagoscopy or esophagraphy. Esophageal varices were unequivocally demonstrated in 5 of 10 patients, examined because of clinical evidence of cirrhosis and a history of upper gastrointestinal hemorrhage, and in whom the varices had not been previously denoted by standard diagnostic methods. Positive splenoportographic evidence of an intrahepatic space-filling lesion was found in 13 of the 20 patients examined for neoplasms of the liver. This technique is helpful in demonstrating cysts or pseudocysts in those persons suspected of having

lesions of the pancreas. Of 7 patients with advanced intra-abdominal carcinomatosis, 5 had positive splenoportographic findings and were proved to have advanced primary carcinomas of the stomach. All of the patients examined in the group suspected of having benign lesions, except one, were found to have normal splenoportographs, while the whole group was later proved to have had benign lesions. Splenoportography does provide more direct and comprehensive information regarding the pathology and anatomy of the portal venous system than any other method, with the exception of direct portal venography. The infrequency of complications and the relative absence of disturbing sequelae of any magnitude, concomitant with the tenet that this type of examination is no more disturbing to the patient than most endoscopic or angiographic procedures, is ample justification for its continued use as a diagnostic tool of no small import.

Determination of Success After Mitral Valvotomy: Role of Circulatory Obstruction of the Myocardium and of Other Factors. P. Mounsey. Brit. M. J. **2**:311-318 (Aug. 10) 1957 [London].

The progress of 100 patients, 2 to 6 years after mitral valvotomy, has been examined, and the relative importance of circulatory obstruction, the state of the myocardium, and other factors in determining clinical improvement have been assessed. Success after mitral valvotomy, maintained in the long-term follow-up period, was related to the degree of surgical success in removing obstruction to blood flow through the mitral valve. A short remission of symptoms was often obtained in patients in whom only a small amount of enlargement of the valve had been effected, but in the 3rd and 4th years the conditions of many of these patients began to deteriorate. Calcification of the mitral valve, when extensive, presents an added obstructive factor in mitral stenosis. The stenosis is due as much to rigidity of the cusps as to fusion of their commissures. In the long-term follow-up period most of these patients have had disappointing results, especially those patients in whom extensive calcification of the stenosed valve was associated with moderate incompetence. Associated aortic stenosis of severe degree was present in 1 patient treated by mitral valvotomy alone. Relief of circulatory obstruction of the mitral valve precipitated left ventricular failure and death. The physical signs of this lesion may be partly masked by the associated mitral stenosis. The clinical improvement of patients with and without pulmonary hypertension differed little, if allowance is made for other causes of deterioration. Although some of the patients have shown electrocardiographic evidence of regression of hypertension, in none has the electrocardiogram returned to normal. None of the patients has presented acute rheumatic carditis after the operation. It is unlikely that active rheumatism played any part in influencing the response of the myocardium to circulatory obstruction. The degree of cardiac enlargement is one index of the state of the myocardium. The best results after valvotomy were seen in patients with smaller hearts, especially those who were young and in sinus rhythm. Satisfactory progress, however, was often seen in older patients in atrial fibrillation and with larger hearts.

A functional reaction to the preoperative symptoms usually tended to hinder and delay improvement. Bronchitis, although often alleviated by successful valvotomy, tended to recur in some patients during the long follow-up period. Patients with severe emphysema combined with bronchitis followed a uniformly downhill course. Mitral valvotomy in the presence of massive intra-arterial thrombosis was followed by fatal cerebral embolism in 3 patients. Radiographic examination revealed calcification in the wall of the left atrium in 2 of these patients. Such patients probably require an open operation. A recent history of systemic emboli was considered an indication for valvotomy, since removal of obstruction to the circulation diminishes the likelihood of clot formation; embolism recurred after valvotomy in 1 of 10 such patients. Associated mitral incompetence did not influence postoperative progress, except in the presence of a heavily calcified mitral valve. Aortic incompetence was of sufficient degree to modify the success of the operation in 1 patient only. Tricuspid incompetence developed for the first time after operation in 6 patients and did not seriously detract from clinical improvement except in 1 patient.

Plastic Grafts for Aortic Substitution in Man. H. B. Shumacker Jr. A. M. A. Arch. Surg. **75**:413-422 (Sept.) 1957 [Chicago].

Ninety-two cases form the basis of a report which includes 61 cases of aneurysm of the abdominal aorta, 8 of aneurysm of the thoracic aorta, 5 of coarctation of the aorta, 12 of arteriosclerotic occlusive disease, and 6 miscellaneous cases. A thin nylon cloth, which had been found satisfactory for the closure of experimentally produced cardiac septal defects and had been rendered impervious, or nearly so, by heat fusion of a thin layer of polyethylene (Polythene) between 2 layers of the cloth, was employed for aortic or aortic bifurcation replacement in 13 clinical cases. The same nylon fabric, coated with a film of methyl methacrylate, was used in the treatment of a 75-year-old man with a large abdominal aortic aneurysm to bridge a defect from the aorta just below the renal arteries to both common iliac arteries. It has functioned well, the patient remaining in good health. Experimental studies found the nylon filter fabric and the braided nylon tubular grafts of Edwards and Tapp far superior to the grafts made of fused nylon and

Polythene and to grafts coated with methyl methacrylate. They were also judged superior to homografts, inasmuch as they did not undergo late degenerative changes. Such grafts were employed in 58 clinical cases, working well in all of them. Braided-nylon tubular grafts sutured to one or both iliac extensions of a Y-shaped filter-fabric graft, where it was necessary to insert one or both ends of the graft into the distal femoral artery, worked well in 5 of 6 cases. Braided-nylon tubular grafts were used in 14 patients, a straight crimped graft in 6, and bifurcation grafts placed either end-to-end or end-to-side to the aorta and the femoral or popliteal arteries. These proved satisfactory. Although experimental studies indicate that nylon tends to lose strength during the first few months after implantation to a greater degree than do other plastic materials, it would seem that the initial strength of the nylon grafts is sufficient to prevent aneurysmal dilatation. One instance of prolonged and troublesome bleeding through a bifurcation Edwards-Tapp graft (since improved) may have been responsible for a patient's death. The hospital mortality for the 92 patients in whom plastic grafts were used for aortic substitution is as follows: abdominal aortic aneurysm not ruptured or complicated by previous myocardial infarction, 2 (5%); ruptured abdominal aortic aneurysm, 7 (54%); abdominal aortic aneurysm with previous myocardial infarction, 5 (45%); arteriosclerotic occlusive disease, 1 (8%); coarctation of the aorta, 1 (20%); thoracic aortic aneurysm, 6 (75%); and miscellaneous, 4 (67%).

Diagnosis and Treatment of Aganglionosis of the Myenteric Plexus. W. L. Riker. A. M. A. Arch. Surg. **75**:362-376 (Sept.) 1957 [Chicago].

Many reports state that 90% of the cases of aganglionosis of the myenteric plexus are of the short-segment type, involving only the rectosigmoid, and 10% are of the long-segment type, involving more than the rectosigmoid, whereas in the present report over 40% of the cases involved the intestine above the rectosigmoid, and 2 patients are included in whom the pathology extended from the anus to the duodenum. Of 22 patients with severe obstruction in the neonatal period, the aganglionosis was of long-segment type in 12, extending to the splenic flexure in 1, to the transverse colon in 6, throughout the colon in 2, and up to the duodenum in 2. Complete or partial intestinal obstruction, vomiting of bile, abdominal distension, and failure to pass stools are symptoms peculiar to various serious disorders in the newborn. Possibilities to be considered include stenosis and atresia of the intestine, meconium ileus, meconium peritonitis, imperforate anus, malrotation of the intestine, and duplication of the intestine. Upright and supine roentgenograms of the abdomen showing signs of obstruction with gas-filled, distended loops of intestine and air-fluid levels, further identified as colon concomitant with a rectum free of gas and feces, are indicative of aganglionosis. Typical roentgenographic findings of a narrow rectosigmoid colon and an abrupt transition of dilated colon have been demonstrated in only 5 infants in the neonatal period, although Berman reports positive colon fluoroscopic findings in 15 of 19 patients less than 5 weeks of age as evidenced by the presence of a transition zone or prolonged retention of barium in the colon. Twelve of 24 patients treated during the neonatal period required surgery within the first week of life; the remainder recovered sufficiently from their acute obstruction to be sent home, only to be plagued by constipation or diarrhea, intermittent vomiting, dehydration, and malnutrition until they returned for surgery within a few weeks. The classic history and findings associated with megacolon are not enough, since partial mechanical obstruction and idiopathic or acquired megacolon may give the same clinical picture. Fluoroscopic examination of the rectosigmoid with a barium enema will establish the diagnosis in most instances. Only one false-negative and no false-positive results of barium enemas were encountered. The association of other congenital anomalies with congenital megacolon was relatively infrequent; however, 6 children in this series did have a familial history of megacolon. The high mortality rate with medical management, especially in the younger age group, suggests that a conservative program should be used only in mild cases that respond well to a regimen of drugs, dietary management, and occasional enemas. An exploratory laparotomy and biopsy of the rectosigmoid colon should be followed in 6 months by resection of the descending colon and a pull-through anastomosis, while in the older age group a primary resection and pull-through anastomosis should be done.

Experiences with Aortic Dissecting Aneurysms. C. Lyons and W. S. Edwards. Am. Surgeon **23**:520-528 (June) 1957 [Baltimore].

The diagnosis of dissecting aneurysm of the aorta was an academic exercise of little practical help to the patient until DeBakey and his associates described a technique of dividing the thoracic aorta, obliterating the false passage below by approximating the inner and outer layers, and excising a window in the intimal and medial layer above and reanastomosing the 2 ends, thus creating a reentry from the outer false passage into the normal lumen and obliterating the distal passage. The first patient represented a fairly typical case of dissecting aneurysm, with paroxysmal, burning chest pain at the lower part of the sternum going up to the neck; marked fatigue in buttocks and legs; blood pressure of 140/110 mm. Hg in right arm, 210/110 mm. in

left arm, 135/60 mm. in right leg, and 0 in left leg; faint left carotid pulse and strong right carotid pulse; and a rapidly narrowing descending thoracic aorta adjacent to a less well-visualized channel comprising the remainder of the descending aortic mass. The diagnosis was confirmed by aortography. Surgical intervention through the bed of the 6th rib, with subsequent transection of the aorta, revealed a false channel dissecting about one-third of the circumference of the aorta anteriorly. This false channel was collapsed, the dissected intima sutured to the media and adventia, and the 2 aortic segments approximated with a continuous running suture. This patient, discharged on therapy with 2 mg. of reserpine daily and moderate salt restriction, was reported doing well symptomatically 3 months later, but manifested blood pressure in the range of 200/90 mm. Hg in spite of continued reserpine administration. The second patient presented variable physical signs which were interpreted, in the absence of aortography, by a combined surgical-medical cardiovascular review to be best explained on the basis of dissecting aneurysm of the aorta. No dissecting aneurysm of the aorta was found at operation, and it was thought in retrospect that the cause was obstruction of the left subclavian artery and possibly of the left carotid by atheromatous plaques or arteriosclerotic narrowing with obliterative arteriosclerotic obstruction of the abdominal aorta or common iliac vessels. A preoperative diagnosis of dissecting aneurysm distal to a coarctation was made in the third patient, surgery revealing a constriction almost 2 cm. distal to the left subclavian artery with a huge poststenotic aneurysm extending almost to the diaphragm. The coarctation and the aneurysm were freed, and the aorta was resected from 1 cm. below the subclavian artery to the diaphragm and replaced with a 7-in. lyophilized homograft, which was sutured end-to-end. The above case is believed to be the first reported successful cure of this rare type of dissecting aneurysm.

Management of Symptomatic Aganglionic Megacolon in Early Infancy. W. K. Sieber and B. R. Girdany. A. M. A. Arch. Surg. **75**:388-397 (Sept.) 1957 [Chicago].

Experience in the treatment of 30 infants with symptomatic aganglionic megacolon has shown the serious nature of the problem and indicated that prompt colostomy to relieve obstruction must take precedence over medical and drug therapy. Five male and 25 female infants, all of whom were products of normal gestation and had normal birth weights, comprised the group. There was only one instance of familial disease. Histological examination confirmed the diagnosis of aganglionic megacolon in all patients, 17 of whom were admitted to the hospital before they were one month of age. The aganglionic area extended to the terminal ileum, including the entire colon, in 2 female infants, from the anus to the transverse colon in 6, and from the anus to various levels in the rectum and sigmoid colon in the remaining 22 infants. One infant presented accompanying malformations of the intestinal tract, consisting of ileal stenosis and malrotation of the midintestine. Another was Mongoloid. None of the 30 had associated genitourinary anomalies. In the group studied, 8 infants had a history of obstipation with gradually increasing abdominal distention, 13 had complete intestinal obstruction from birth, and 9 infants had intermittent partial intestinal obstruction. Of the 30 infants 18 survived. The 1 death in the group of 8 infants who had obstipation and episodes of acute intestinal obstruction occurred in an infant with aganglionosis of the entire colon. Of 13 infants with complete obstruction at birth, 5 died, and of the 9 infants with intermittent severe obstruction, 6 died. Autopsy findings disclosed phlegmonous colitis in 2 infants, pseudomembranous colitis in 2, error of technique either in performance or in selection of the appropriate operative procedure in 5, and inanition and starvation following chronic colonic obstruction in 3.

Aganglionic megacolon should be suspected in any infant with signs of complete or partial obstruction, progressive abdominal distention, and scanty stools. Roentgen examination allows a definitive diagnosis. The lateral film of the abdomen shows a tiny-calibered, air-containing rectum and dilated loops of air-containing intestine distending the abdominal cavity. Plain film examination has suggested the diagnosis in 27 of the 30 infants. Contrast studies with use of Dionosil-saline mixtures (barium mixtures are contraindicated) permit definition of the caliber of the distal colon and the site of transmission and aid the surgeon in the selection of the site of colostomy. The differential diagnosis of symptomatic aganglionic megacolon in early infancy includes all cases of low intestinal obstruction, tracheoesophageal fistula without esophageal atresia, celiac disease, and primary peritonitis. Prompt surgical intervention is advocated, as prolonged nonsurgical treatment rarely accomplishes lasting improvement after the infant with aganglionic megacolon has experienced an episode of intestinal obstruction. "Conservative" management leads to a state of severe malnutrition, inanition, chronic colonic obstruction, the disappearance of subcutaneous fat, recurrence of pulmonary infections and phlegmonous colitis. Prolonged medical therapy to prepare the infant for surgery did not accomplish its purpose; surgery had little to offer after the obvious failure of medical regimens. The infant with the intestinal obstruction was in better condition for surgery then than at any other time. Prompt colostomy immediately proximal to the aganglionosis, the treatment of choice in symptomatic agan-

glionic megacolon in early infancy, done as an emergency measure, is lifesaving and affords an excellent prognosis in the absence of phlegmonous colitis, inanition, intestinal perforation, or septicemia.

Infections Complicating Gastric Surgery: II. The Mechanism of Postoperative Peritonitis. O. Sahlin and C. F. Högman. Acta chir. scandinav. **113**:79-95 (No. 2) 1957 (In English) [Stockholm].

The authors report on 94 patients with duodenal and gastric ulcer or nonmalignant gastric tumor who were operated on. Billroth 2 was performed in 81 patients, 65 of whom had duodenal and 16 of whom had gastric ulcer. Billroth 1 was performed in 2 patients with duodenal ulcer and in 1 with gastric ulcer. Subtotal gastrectomy with jejunal replacement was performed in 6 patients with gastric ulcer. Excision of a nonmalignant gastric tumor was performed in 3 patients, and gastroenterostomy in 1 with duodenal ulcer. At operation, enlarged lymph nodes were removed from the pyloric region or the omentum before the actual resection was started. The resected specimen yielded samples of the gastric contents, the ulcer crater, and the ulcer wall for bacteriological examination. Postoperative sampling was performed with the aid of duodenal, abdominal, and gastroenterostomy tubes. Bacterial growth was noted in 7 of the 42 lymph nodes examined. The bacteria were pathogenic in 2 lymph nodes. Postoperative bacteriological examination of intra-abdominal samples gave positive results in 50% of the cultures. A successive increase in culture-positive samples was noted during the first postoperative week.

Antibiotic prophylactic treatment was given from the day of operation to 28 patients (30%). The incidence of culture-positive samples was 45% in patients who had not been given antibiotics, 35% in those who were given penicillin and streptomycin, and 85% in those treated with oxytetracycline, penicillin, and streptomycin. The bacteria found after the operation in the abdominal cavity of patients who had been given prophylactic treatment with antibiotics were more resistant in vitro than those recovered from patients not so treated. There was definite correspondence between the bacteria isolated from intra-abdominal specimens and the coexistent bacterial flora of the upper portion of the alimentary tract.

During the first week after gastric resection, bacteria pass through the anastomosis and the duodenal stump in a large number of patients without any clinical signs of complication. Thus, subclinical peritonitis may be assumed to be present in most patients. This condition cannot be prevented by the administration of antibiotics. Furthermore, the antibiotics produce an increasing incidence of resistant strains in the bacterial flora. A local inflammatory process involving the anastomosis may have been one of the chief causes of postoperative gastric retention which occurred in 7 of the 94 patients and in 3 additional patients operated on by other workers. Five of the patients with retention had received prophylactic treatment with antibiotics from the day of operation. Two of these, and 2 other patients who had not received antibiotics, later underwent reoperation for total retention. Antibiotic therapy was administered to these 4 patients, without effect on the retention or the subfebrile temperature. The cases of the 4 patients are reported in detail; they support the assumption that the inflammatory process involving the anastomosis was of infectious origin and that it developed in the absence of any insufficiency of sutures.

Staphylococcal Enterocolitis. E. Lepley Jr. and M. B. Smith. A. M. A. Arch. Surg. **75**:377-387 (Sept.) 1957 [Chicago].

The clinical picture of micrococcic (staphylococcic) enterocolitis, described as "choleriformic syndrome," includes the patient who, though doing well in the immediate postoperative period, suddenly becomes anorexic, complains of abdominal pain and distention, has a pulse rate rising to 130 to 150 per minute, and becomes lethargic or semicomatose. The patient may complain of dyspnea and a sore throat and/or tongue, which may be preceded or followed by a severe watery diarrhea (rice-water stools) resulting, if unchecked, in severe massive electrolyte and fluid loss, and ultimately oliguria. Mild hypotension may be present early and is capable of progressing to circulatory collapse, which, if prolonged, may become irreversible. The disease entity would appear to be a superinfection, occurring with increased incidence and concomitant with widespread antibiotic therapy. The etiological agent is an antibiotic-resistant, coagulase-positive hemolytic Micrococcus (Staphylococcus) pyogenes var. aureus. In the case of a patient operated upon for correction of gastrointestinal pathology, who has received preoperative and/or postoperative antibiotics for prophylaxis or treatment, the following sequence is postulated: (1) the patient is a carrier of virulent micrococci which are resistant to the antibiotic being used; (2) the normal flora of the intestine is suppressed or eliminated by the antibiotic and the resistant micrococci, usually suppressed by the intestinal flora, flourish; (3) the flourishing micrococci elaborate an enterotoxin, producing severe toxicity; (4) the micrococci invade the intestinal wall, causing mucosal necrosis and massive extravasation of fluid into the lumen of the intestine and severe diarrhea; and (5) the fluid and electrolyte losses become massive, resulting in hypovolemia and circulatory collapse. Of 16 patients with micrococcic enterocolitis, all of whom

were males ranging in age from 40 to 77 years, all but one had been treated from some involvement of the gastrointestinal tract.

The disease occurred in the postoperative period in all but 2 of the 16 patients, in whom no secondary disease pattern was demonstrable except for dental caries and pyorrhea uncorrected prior to operation. In this group of patients, 12 of the 16 received preoperative antibiotics in the form of neomycin, bacitracin, penicillin, or streptomycin, singly or in combination with chemotherapeutic agents, such as succinylsulfathiazole or phthalylsulfathiazole. All of the patients received antibiotics postoperatively. All micrococci isolated from stools after the onset of enterocolitis were resistant to the antibiotic being used, except for the single instance in which chlortetracycline was given. No pattern of sensitivity was demonstrable, with the exception that in 14 of the 16 cases the strains were chloramphenicol sensitive. The prerequisites for the development of micrococcic enterocolitis are (1) intestinal pathology, (2) suppression of normal intestinal flora with antibiotics, (3) overgrowth of resistant micrococci, and (4) cross infection as the source of the pathogen. Bacteriological studies on the patients and staff of a hospital after the fatal termination of 2 cases of enterocolitis revealed 7 patients and 1 staff member as carriers of 17 strains of virulent M. aureus. The treatment of enterocolitis is recommended as follows: (1) withdrawal of the antibiotic being used, (2) treatment with the antibiotic to which the micrococci are most sensitive, (3) immediate replacement of fluids and electrolytes and use of blood or plasma expanders as indicated, and (4) close and continuous supervision.

Surgery in Haemophilia: The Use of Animal Antihaemophilic Globulin and Human Plasma in Thirteen Cases. R. G. Macfarlane, P. C. Mallam, L. J. Witts and others. Lancet **2**:251-259 (Aug. 10) 1957 [London].

There is evidence that the abnormal bleeding of hemophilia is due to the hereditary deficiency of a normal clotting factor named antihemophilic globulin. Since human blood is not likely to be adequate for daily use in the prophylactic treatment of hemophilia, work at Oxford has been concentrated on the extraction of antihemophilic globulin from animal blood. Observations are described on 13 hemophilic patients undergoing surgery or dental extractions while being treated with antihemophilic globulin concentrated from bovine or pig blood. The average dose of 200 to 400 mg. was equivalent in activity to about 2,500 ml. of fresh human plasma. There was no abnormal bleeding in any of the patients while the level of antihemophilic globulin in the blood was above 30% of the normal, but in some patients there was great variation in the doses required to maintain this level. In the case of clean wounds the temporary raising of the antihemophilic globulin level by 1 or 2 injections might be followed by complete healing without hemorrhage. In large or infected wounds bleeding might recur if the blood antihemophilic globulin level fell below 30%. The material is probably antigenic, since after 10 to 14 days' treatment with bovine or pig antihemophilic globulin mild allergic reactions sometimes occurred after each injection. In 4 cases the alternative preparation was then given for a further period without cross-reaction and with good hemostatic effect, but one patient failed to respond to the second preparation. The antigenicity is probably low, because skin tests remained negative, and no antibodies or anticoagulants active against the antihemophilic globulin used could be demonstrated in the blood of the patients.

The allergic reactions encountered were controlled by antihistaminic drugs. The one serious (anaphylactic) reaction observed was found to be due to previous sensitisation of the patient by a proprietary hemostatic of bovine origin. Serum sickness was not seen in any patient. No adverse after-effects, no increased hemorrhagic tendency, and no decreased response to transfusion of human blood was observed. Animal antihemophilic globulin proved lifesaving in at least 3 of the cases, but, like antitoxins and other serums of animal origin, it is potentially dangerous in its present form. The risk of anaphylaxis contraindicates a second course of the same preparation in the same patient. Animal antihemophilic globulin should not be used, therefore, unless the patient's life is in danger: once it has been given, he is deprived of a treatment which might be required in some future emergency. The rapid transfusion of large volumes of human plasma has allowed performance of major and minor surgical operations without undue bleeding in many hemophilic patients. An important part of the treatment was the immobilization of wound area and avoidance of all procedures likely to cause trauma until a hemostatic level of antihemophilic globulin was obtained. Future work on the treatment of hemophilia should be concerned with nonantigenic, antihemophilic factors from the crude antihemophilic globulin now obtainable from human and animal blood.

Causalgia. J. C. Owens. Am. Surgeon **23**:636-643 (July) 1957 [Baltimore].

A bizarre symptom-complex designated as causalgia is occasionally observed after accidental or surgical injuries. The term was first used by Weir Mitchell in 1872, but the condition has been described also under various other terms, such as neurovasospastic phenomenon, reflex nervous dystrophy, Sudeck's atrophy, and traumatic vasospasm.

To emphasize the variety of initiating causes, the author presents observations on 50 patients with causalgia. The outstanding feature of the disorder is burning superficial pain. The superficial character is especially emphasized to differentiate it from deep pain, such as that caused by ischemic neuritis, traumatic neuritis, abscess, neuroma, and bone injury. The pain may be described as throbbing, aching, or vise-like.

Hyperesthesia is the second most prominent complaint. This may be localized to a sensory nerve. Slight stimuli, such as drafts, bed-sheets, or examiners' hands, will induce extreme paroxysms of pain. To protect the injured part from such stimuli, patients sometimes hold the extremity in one position and cover it with dry or moist cloths. There may be increased sweating. Vasomotor changes vary widely. Warm rubor may develop into the pale, cool, wet foot. Patients with arteriosclerosis may show the shiny, scaling, dry foot. Diagnosis is generally based on (1) history of overactive sympathetic nervous system, (2) superficial pain exceeding the expected, and (3) hyperesthesia localized to a sensory nerve. Treatment consists of intra-arterial and/or oral sympatholytic drugs, paravertebral sympathetic blocks, or sympathectomy, plus physiotherapy. Recognition of the syndrome is important, since these patients are miserable, and organic changes may take place over a period of time. Such persons are frequently misunderstood because the source of the symptoms is not realized.

Tissue Necrosis Associated with Intravenous Nor-epinephrine Administration. R. R. de Alvarez, L. M. Nyhus, K. A. Merendino, H. N. Harkins and R. K. Zech. Am. Surgeon **23**:619-635 (July) 1957 [Baltimore].

Epinephrine has been surpassed by its isomer l-nor-epinephrine as a pressor agent. Nor-epinephrine, a catechol amine, exerts its effect by producing generalized arterial, capillary, and venous constriction, thereby resulting in a marked increase in systemic blood pressure. Nor-epinephrine is also an effective adjuvant in the therapy of acute renal failure secondary to vasomotor collapse. Ulceration of the skin and deep subcutaneous structures occurs, however, as a result of the drug's marked vasoconstrictive properties. The authors present 9 representative case histories, which leave little doubt as to the destructive possibilities of the drug. It was found that nor-epinephrine in concentration of 4 to 8 mg. per liter produces marked local tissue necrosis in human subjects. Furthermore, nor-epinephrine, when infused intravenously, produces marked generalized vasoconstriction with ischemic tissue necrosis at points remote from the site of infusion. With regard to this last point, the authors differ from most other observers. In one of the patients presented, a necrotic area developed on the hand, and in another, on the conjunctiva after the use of nor-epinephrine solution. Therapy of tissue damage from nor-epinephrine solution is most effective if it is instituted early. Local application of heat is inadvisable because cellular metabolic requirements are increased without concomitant vasodilatation. Injection of hyaluronidase and 1 or 2% procaine into the affected area aborted the persistent ischemia in some cases before permanent damage occurred. The authors had exceptionally good success with the use of mecholyl iontophoresis.

Since many other conditions existed in patients in whom tissue necrosis occurred, it was thought desirable to explore the possibilities of causation of the tissue ulceration with these conditions operating. Studies were made on groups of dogs to ascertain the role of such factors as the intradermal escape of the drug, the local pooling of nor-epinephrine solution, the use of polyethylene cannulation, the presence of shock, the presence of blood loss prior to shock, and tissue tension, as well as the influence of extravasation of the nor-epinephrine as a complication of intravenous administration. These studies demonstrated that nor-epinephrine, as generally administered for the control of vasomotor collapse, is an extremely potent vasoconstrictor. Only local ulceration could be produced at the site of nor-epinephrine leak; distant ulceration could not be identified. Intradermal administration of nor-epinephrine did not result in local ulceration. Significant ulceration appeared in 2 dogs when nor-epinephrine was administered subcutaneously to a point of tension. Under conditions of shock no tissue ulceration occurred in dogs following the intravenous administration of nor-epinephrine. Perhaps vasomotor influences, which would increase vascular permeability, were not operating in sufficient degree or sufficient duration to allow extravasation. Following intravenous administration of nor-epinephrine, extensive, deep tissue necrosis and ulceration occurred only at the site where extravasation of nor-epinephrine was permitted. While nor-epinephrine is lifesaving under certain circumstances, local and remote effects should be watched for.

Coma with Increased Amino Acids of Brain and Cerebrospinal Fluid in Dogs with Eck's Fistula: Prevention by Portal-Systemic Collateral Circulation. J. L. Bollman, E. V. Flock, J. H. Grindlay and others. A. M. A. Arch. Surg. **75**:405-412 (Sept.) 1957 [Chicago].

Animals with Eck's fistula have a patent portacaval shunt with no blood entering the liver by the portal vein. In the absence of changes in collateral circulation they have typical symptoms and die within a year. When such dogs maintain their

weight and show no symptoms, they are found to have a closed portacaval shunt, with portal collateral vessels bridging the ligature of the portal vein so that portal blood is reaching the liver or collateral portal-caval circulation. Occlusion of the vena cava above the portacaval anastomosis results in caval blood being diverted into the portal vein and the subsequent development of portal-systemic collateral circulation, which markedly alters the course of animals with Eck's fistula.

Portacaval anastomosis with complete ligature of the portal vein was followed by typical symptoms and coma. Partial occlusion (two-thirds) of the vena cava above the portacaval anastomosis upon the appearance of coma resulted in the immediate recovery of these animals, with regaining of weight and disappearance of symptoms. Occlusion of the vena cava below the portacaval anastomosis of an animal with adequate portal-systemic collateral circulation and an occluded portal vein resulted in loss of weight, the appearance of typical Eck's fistula symptoms, and death within 3 months. This illustrates the fact that the course and symptoms of animals with Eck's fistula is dependent on some factor other than portacaval shunt and subsequent diversion of portal blood from the liver. A study of samples of cerebrospinal fluid withdrawn from 20 dogs during coma caused by Eck's fistula revealed total free amino acid levels to be normal in 7, twice normal in 7, three times normal in 3, and four times normal in 3, the increase generally being in glutamine. No single amino acid was predominantly increased, with the exception of glutamine. No correlation was found to exist between the changes in amino acids and the length of the postoperative period in dogs with Eck's fistula, the degree of loss of weight, or the duration or intensity of coma just prior to withdrawal of the cerebrospinal fluid. No appreciable increase of free amino acid content was demonstrable in the plasma of dogs with Eck's fistula, even in those dogs in whom there were large increases in the free amino acid content of the brain and cerebrospinal fluid. Electroencephalographic studies showed a definite difference between the coma of animals with Eck's fistula and the coma of hepatectomized animals. None of the electroencephalographic recordings of animals with Eck's fistula differed appreciably from previous recordings of the same animals, except for the appearance of a "seizure pattern" in the extremely late lethal phase of the attacks. Electroencephalographic recordings during the coma of hepatectomized animals indicated a slowing of the brain waves and the appearance of triphasic waves similar to those seen during hepatic coma in humans. The typical electroencephalographic recording in coma induced by intoxication with ammonia differs from that seen in the coma associated with Eck's fistula or the coma of hepatic deficiency.

NEUROLOGY & PSYCHIATRY

Paroxysmal Abdominal Pain as a Manifestation of Epilepsy. J. L. O'Brien and E. S. Goldensohn. Neurology **7**:549-554 (Aug.) 1957 [Minneapolis].

During the study of a 9-year-old girl with recurrent bouts of abdominal pain in whom the diagnosis of abdominal epilepsy was suspected, the authors had the opportunity to obtain an electroencephalogram while the patient was experiencing an attack. While several authors have described abnormal cortical electrical activity between attacks of abdominal epilepsy, the present case and one described by Livingston demonstrate electroencephalographic abnormalities recorded during the seizure itself. In both instances the resting records were considered to demonstrate some degree of abnormality. Between the episodes of abdominal epilepsy the record contained suggestive paroxysmal features. During the attack the record consisted of runs of partly synchronous high voltage 3 cps waves in all leads. It is possible that pain is primary in some cases of abdominal epilepsy, while in others it is secondary to abnormal gastrointestinal motility. In most instances the etiology is obscure. Symptomatic treatment with anticonvulsants is effective.

Myasthenia Gravis Appearing After the Removal of Thymoma. L. P. Rowland, H. Aranow and P. F. A. Hoefer. Neurology **7**:584-588 (Aug.) 1957 [Minneapolis].

The histories of 3 patients are presented in whom myasthenia gravis appeared after the removal of a thymoma. Analysis of the clinical and pathological features of these patients and of 7 similar cases reported from other centers makes it seem unlikely that the thymic tumor causes the myasthenia, but it does not completely exclude the possibility that some thymic abnormality is responsible. It seems more likely that both the histological changes in the thymus and myasthenia gravis result from a common cause.

Epidemic of Nonbacterial Meningitis in Aachen. E. Scheidhauer, W. Brodel and K. Röttger. Ärztl. Wchnschr. **12**:712-715 (Aug. 9) 1957 (In German) [Berlin].

The authors report on 268 patients with nonbacterial meningitis who were hospitalized in Aachen, Germany, in the summer of 1956. The average age of the patients was 18 years. The clinical aspect of the disease showed great conformity in children, adolescents, and adult patients. There was a sudden onset with fever, exhaustion, nausea, vomiting, headache, and occasionally abdominal pain. Chills did not occur. A diphasic course with a second bout of fever after 2 or 4 days of subfebrile temperatures was observed in many patients, and

the average duration of fever including the subfebrile interval varied from 6 to 14 days. Vomiting was more severe in children than in adolescents and adults. The headache was frontal and orbital. A mild conjunctivitis with photophobia and pain associated with ocular movements was frequently observed. Headache subsided soon after lumbar puncture. The second phase of the disease was usually milder, and headache subsided without repeated lumbar puncture. A large number of children had a herpangina-like eruption on the soft palate and on the anterior palatine arches, but these lesions disappeared after several days. Swelling of the lymph nodes at the angle of the jaw occurred in 50% of the children. An eruption on the face and trunk similar to that of German measles or scarlet fever was observed in only 22 children and 2 adults. Reflexes were normal in most of the patients; diminished reflexes in 9 children and in a few adults and increased reflexes in a larger number of patients were observed only for a short time.

The diagnosis of nonbacterial meningitis was based on the clinical findings and on the results of lumbar puncture. The cerebrospinal fluid escaped with normal or slightly increased pressure, and the average number of cells was 2,187 per cubic centimeter. A mild pleocytosis persisted for several weeks, but the cerebrospinal fluid usually was restored to normal within 5 weeks. Culture and animal experiments gave negative results. The blood picture was not characteristically changed. The blood sedimentation rate was slightly increased in the beginning but was restored to normal within 8 to 14 days. Treatment consisted of the administration of sedatives, antipyretics, and analgesics. The age of the patients suggested a tendency toward the occurrence of the disease in young patients, and a seasonal disposition was suggested by the epidemic's occurrence between June and September. The prognosis was favorable. The disease seemed to be highly contagious, since several members in the same family were frequently affected. Differential diagnosis of nonbacterial meningitis from poliomyelitis was made with the aid of the complement fixation reaction, which gave negative results in most of the patients. A virus which seemed to belong to the Coxsackie-A group is considered as the causative agent of the nonbacterial meningitis.

Psychosomatic Disorders in Pilot Trainees: Report of Nine Cases. P. B. Phillips. J. Aviation Med. **28:** 364-369 (Aug.) 1957 [St. Paul].

No screening devices for selecting candidates for flight training have yet been developed which eliminate those who may fail because of their reaction to stress experienced during actual flight training. Flight surgeons examining applicants for flight training are prone to pass the questionably stable candidates hoping they will somehow measure up in the training program, although they are aware that certain personalities manifest ego defenses against anxiety which are not compatible with success in an aviation career. In the Naval Air Training Command at Pensacola, Fla., a good cross section of the hazardous and often disqualifying reactions which students experience has been observed. The varied reactions to the stress of early flight training and the hazards such reactions impose are illustrated on the basis of 9 case histories. No effort was made to determine the dynamics behind the specific symptom.

Symptoms pointed up by this study include low G tolerance, hyperventilation, "vertigo," headache, nausea and vomiting, delayed reaction time, unconsciousness, "clouding of consciousness," confusion, unsteadiness, blurred vision, and constricted visual fields. All patients had what was believed to be an adequate medical examination, and the conclusion of trained flight surgeons was that these were all primarily symptoms of anxiety. It is not contended that all anxiety is necessarily bad, because controlled anxiety enhances the alertness and effectiveness of an aviator. But many of the manifestations of anxiety are such as to increase the real hazard of flying and contribute to the unexplained accident. Only by close contact with instructors and students can flight surgeons identify the student aviators whose symptoms make them poor risks for aviation careers. Physicians in aviation medicine must be on the look-out for psychosomatic manifestations of anxiety that may lead to accidents.

Encephalomyelopathy in Behçet's Disease: Report of Necropsy Findings in Two Cases. W. H. McHenemey and B. J. Lawrence. Lancet **2:**353-359 (Aug. 24) 1957 [London].

Neurological lesions in 1 case of Behçet's disease were widespread and advanced, involving the upper brain stem, basal ganglions, and the cerebral cortex. Major ischemic lesions were found in the left temporal and occipital lobes, and seemed to be of 4 types: (1) foci of softening in relation to blood vessels with moderate microglial activity, rather feeble astroglial proliferation, and, when involving grey matter, loss of nerve cells; (2) perivascular cellular infiltrations with lymphocytes and occasional microglial cells, mostly in the white matter and with slight associated loss of myelin; (3) perivascular cuffing with sudanophilic foam-cells, mostly in the white matter; and (4) extensive and patchy areas of cortical infarction with consecutive atroglial proliferation. Neurological lesions in another case were neither as plentiful nor as advanced, being largely confined to the upper brain stem. The immunity of the cerebellum in both cases is noteworthy. A

significant feature of Behçet's disease is its geographical predilection for the Eastern Mediterranean basin where Hippocrates first described the endemic disorder now known as the triad of Behçet. The symptomatology in these 2 cases is projected as being due to a series of minor vascular disturbances which could have followed either a thrombosis or some other circulatory insufficiency.

Side-effects of Chlorpromazine Treatment of Psychotic Patients. J. Stousland and H. Sigstad. Tidsskr. norske lægefor. 77:636-638 (Aug. 1) 1957 (In Norwegian) [Oslo].

Although the side-effects in the 196 patients in Eg Hospital treated with chlorpromazine for from 3 weeks to 27 months were numerous, they were transient and of relatively slight clinical significance. No serious complications were observed. By exact clinical control the laboratory tests could be limited to a minimum, which is considered important when the patients are discharged for continued treatment outside the hospital. The condition for discharge must be the establishment of good cooperation between the physician and the patient's family, who must be informed as to the symptoms of possible side-effects of chlorpromazine.

GYNECOLOGY & OBSTETRICS

Folinic Acid in Megaloblastic Anemia of Pregnancy. J. M. Scott. Brit. M. J. 2:270-272 (Aug. 3) 1957 [London].

Folinic acid (Leucovorin) was given to 19 patients with megaloblastic anemia of pregnancy and of the puerperium. In 6 of these patients megaloblasts were found in the peripheral blood, but in the other 13 a confirmatory sternal puncture had to be made. All the patients had severe anemia, and all but one of the pregnancies were complicated by some other condition. Sixteen patients received treament with folinic acid over a limited period, until the reticulocyte response reached its peak. Anemia continued to improve in 11 patients with antenatal anemia, although treatment was discontinued. Folinic acid had to be given in sufficiently large amounts (12 mg. the first day) initially to produce a satisfactory response. The optimum dose was about 6 mg. daily and the total amount was 50 mg. This amount appeared to be necessary, independently of the degree of anemia and the route of administration. It seems unlikely that megaloblastic anemia of pregnancy is due to an absolute deficiency of folic acid. It acts probably as a catalyzer at some stage in the hematopoietic process. With treatment for both the anemia and its complications, the demand for folinic acid may be somewhat reduced, and, with normoblastic erythropoiesis established, the pregnant patient may once more be able to keep herself in balance and maintain satisfactory blood levels.

Sheehan's Syndrome: Anterior Pituitary Insufficiency After Postpartum Hemorrhage. D. Aarskog. Tidsskr. norske lægefor. 77:640-641 (Aug. 1) 1957 (In Norwegian) [Oslo].

Sheehan's syndrome, a subgroup of Simmond's disease, refers to the cases of anterior pituitary insufficiency which develop after postpartum hemorrhage. It is a not wholly infrequent cause of disability in women. It develops insidiously either directly following the puerperium or after a latent period. In the puerperium absence of lactation may be the only symptom. Amenorrhea is an early and fairly constant sign. Libido is lost and atrophy of genitalia and mammae occurs. Loss of pubic and axillary hair is characteristic. The skin becomes smooth and thin. A waxen complexion is common. The patient easily feels cold and perspires little. Psychic changes are frequent, and include asthenia, loss of power of concentration and memory, apathy, and depression. Usually there is only moderate anemia. Blood sugar values are low, and spontaneous hypoglycemia may occur. Insulin sensitivity is increased. In the first of the 2 cases reported there had been 2 uterine ruptures, both of which caused shock. Certain signs of endocrine insufficiency were present after the first rupture. The subsequent pregnancy without any remission of symptoms was remarkable. In the second case mental symptoms dominated. Treatment with cortisone and thyroid brought about complete regression of these symptoms in the first case. In the second case the mental symptoms persisted. Sheehan advises 12.5 mg. cortisone daily, 60 -100 mg. thyroid daily, and 10 mg. methyl testosterone daily. Of these, cortisone is the essential medicament. With this treatment most patients become free from symptoms and fully able to work.

PEDIATRICS

Evaluation of Hyperbilirubinemia as a Guide for the Use of Exchange Transfusions in Hemolytic Disease in the Newborn Infant. M. Pierce and E. Rigor. J. Am. M. Women's A. 12:247-253 (Aug.) 1957 [New York].

The authors discuss the mechanism of hyperbilirubinemia during the neonatal period and present data on the serum bilirubin levels determined in blood samples obtained from the umbilical cord and from the heel at intervals throughout this period in 46 infants with hemolytic disease of the newborn, 31 of whom were treated with exchange transfusions. It was found that clinical assessment of the severity of the disease and the degree of

anemia are more reliable than bilirubin levels in umbilical cord blood for determining the need of exchange transfusion shortly after birth. Serial bilirubin determinations that reveal the rapidity of the progression of hyperbilirubinemia provide reliable criteria for timing the need for the first exchange transfusion and for repeating these transfusions. None of the 46 infants in whom an attempt was made to keep the bilirubin levels under 20 mg. per 100 cc. died from kernicterus. The level exceeded 25 mg. per 100 cc. in only 2 of the patients. Transient signs of mild encephalopathy developed in 1 of the infants in whom the hemolytic process was severe enough to require 5 exchange transfusions.

Clinical Study of Nonerythroblastic Kernicterus in the Premature Infant. A. Hottinger. Semaine hôp. Paris 33:2913-2923 (Aug. 10) 1957 (In French) [Paris].

The new and accurate methods of determining Rh and ABO incompatibility in the infant make it possible to diagnose a form of kernicterus which is rare in the newborn but more frequent in the premature and which cannot be accounted for as a sequel of erythroblastosis. This kernicterus appears in premature infants weighing from 800 to 2,000 Gm. (1.5 to 4.5 lb.) who show signs of severe icterus the 3rd or 4th day after birth. The icterus, which lasts 4 to 6 weeks, differs from the icterus of the newborn infant in color, duration, and other aspects. There is no evidence of hemolysis due to the Rh antigen or ABO immunization. No differences are discernible between this kernicterus and that caused by isoimmunization in anatomopathology, localization, or microscopic appearance. In about 50% of the cases the severe icterus is accompanied by intracranial hemorrhages. Pulmonary infiltration and atelectasis are found in all the patients. Kernicterus may also be found in infants with severe prolonged icterus who have been clinically cured (approximately 16%). Many fatalities occur from the 6th to the 9th day after birth. Infants who recover later exhibit severe cerebral symptoms, such as athetosis and choreoathetosis and other symptoms, such as extrapyramidal symptoms and mental retardation. These children are generally weak, have a high mortality rate, and are often a burden to their families and the community.

The clinical symptoms of infants who die of severe kernicterus closely resemble those of infants with icterus of long duration, but they are different from those of the premature infant with simple neonatal icterus. Bilirubin is the main problem in the pathogenesis of kernicterus. The increase or decrease of the bilirubin content in the blood depends on (1) the destruction of the red blood cells caused by administration or restriction of oxygen, and (2) the clearance function of the placenta and the activity of the liver. This explains to a certain degree the clinical observation that severe icterus often occurs in connection with intrauterine processes promoting anoxia: nephropathy of the mother with placental infarction, placental disease, and premature placental separation. It is also conceivable that after birth hyperoxia encouraging postnatal blood destruction may cause severe icterus. Severe icterus apparently depends on the existence of a bilirubin level of 18 mg. per 100 cc. of serum; apparently it is only the indirect bilirubin that leads to nuclear icterus.

Autopsy revealed pigmentation of the cerebral nuclei with bilirubin. The nervous tissue shows degenerative changes: edema, necrobiosis, and softening. Certain forms of icterus, however, do not lead to kernicterus. Therefore, there must be one or more cerebral factors that permit pigmentation of the cerebral nuclei by bilirubin. This pigmentation may be reversible. Impregnation of the brain by the pigment is facilitated by previous anoxia. Necrobiosis alone cannot be the factor predisposing the patient to kernicterus. Liver function is important. Apparently a system of enzymes separates bilirubin from globin, protects the brain from the indirect and toxic bilirubin, and permits the direct bilirubin to be excreted. Brain immaturity, anoxia, and other still unknown factors predispose the terrain to bilirubin impregnation. Liver immaturity conditions the indirect hyperbilirubinemia which is toxic to the brain of the newborn. Severe prolonged icterus of the premature infant may be cured because the pathological mechanism is reversible to a certain extent. Every influence that increases hemolysis (e. g., vitamin K and oxygen) increases the danger of indirect bilirubinemia.

Phenylketonuria with Normal Intelligence and Gowers' Muscular Dystrophy. S. Coates, A. P. Norman and L. I. Woolf. Arch. Dis. Childhood 32:313-317 (Aug.) 1957 [London].

Phenylketonuria is a rare inborn error of metabolism which is believed to be associated almost always with some degree of mental retardation. The great majority of those affected are idiots or imbeciles; any such patient with an IQ of more than 65 is rare enough to merit reporting. Gowers' peripheral muscular dystrophy is also an unusual disease in children. The patient reported showed this extremely rare combination of Gowers' muscular dystrophy, phenylketonuria, and an IQ of more than 100. The boy had been born at term and at first developed normally. At 3 years of age weakness of the right wrist was first noticed, and at 6 years of age a diagnosis of muscular dystrophy of Gowers' type was made. At the time this diagnosis was made the authors were studying aminoaciduria in muscular dystrophy, and in consequence the urine of this boy was examined by paper chromatography. The concentrations of the ab-

normal indole derivatives in this child's urine were a little above the average, though within the range found for phenylketonuria. Every specimen of urine examined while the child was on a normal diet gave an unmistakable green color when tested with ferric chloride. When the patient was given a diet low in phenylalanine, phenylpyruvic acid, phenyllactic acid, and abnormal indolic and phenolic compounds vanished from the urine, while the concentrations of phenylalanine in the blood and urine dropped to normal, as did his excretion of phenylacetylglutamine.

The daily excretion of phenylpyruvic acid was only about one-quarter to one-seventh of that found in other patients with phenylketonuria, and the excretion of phenyllactic acid was also lower. It is noteworthy that another patient with phenylketonuria with high intelligence also excreted less than the average amount of phenylpyruvic acid, while Følling found a low and intermittent excretion of this acid in some patients with phenylketonuria who were intelligent enough to attend ordinary schools. The idea is inescapable that there is some connection between the higher intelligence and the lower excretion of phenyllactic acid and phenylpyruvic acid. No connection could be found between muscular dystrophy and phenylketonuria. In an addendum the authors say that over a period of 2 years the boy's IQ fell by about 18 points, suggesting deterioration. In view of this and his mother's feeling that he had been better while on a low-phenylalanine diet, this diet was once more instituted.

Peripheral Vasomotor Function in Cretinism. B. D. Bower. Arch. Dis. Childhood **32**:318-324 (Aug.) 1957 [London].

Poor peripheral circulation is a well-known feature of cretinism. To ascertain whether immaturity of the vasodilatation reflex is responsible, studies were made on 5 children who had received no treatment for their cretinism and on 1 child who had been treated. None of the responses to warming of the limb were normal in the 5 untreated children with cretinism. Two of the 3 children with severe cretinism showed no response at all, and the third showed a slow and inadequate response. The patient with moderately severe cretinism showed no response in the feet and a subnormal response in the hand. The child with the mild form of the disease gave a result nearest to normal, although it cannot be regarded as normal since the response improved on treatment. Only the child who had been treated for most of her life with thyroid produced normal responses. In all patients the response became normal during replacement therapy. The possible sites of disturbance of the reflex arc are considered, and reasons are given for postulating that either the hypothalamus or the peripheral vessels themselves are at fault. Whatever the precise anatomic site, the poor peripheral circulation in cretinism is probably, in part at least, due to a failure of skin vessels to dilate in response to warming.

Rickets as a Sequel of Ureterosigmoidostomy. R. Tobler, A. Prader, A. Bühlmann and M. Bettex. Helvet. paediat. acta **12**:215-240 (Aug.) 1957 (In German) [Basel, Switzerland].

During the last 28 years 29 patients with ectopy of the bladder were subjected to ureterosigmoidostomy at the Children's Hospital in Zürich, Switzerland. No dietetic or alkali therapy was carried out after the operation. Twenty-two of the 29 patients were reexamined in 1956 to ascertain metabolic disturbances. Polydipsia, anorexia, tiredness, and stunted growth were present in varying degrees in all of the patients. Analysis of the serum revealed hyperchloremia in 19, hypophosphatemia in 5, and increase in the nonprotein rest-nitrogen in 4 patients. Four of the 22 patients, ranging in age from 6 to 10 years, had roentgenologic and also some clinical signs of rickets. The serum phosphorus content was reduced in all 4 of these patients, but the alkali phosphatase level was increased only in the 1 patient with the most severe form of rickets and with the most severe hyperchloremic acidosis. Retardation of growth was more severe in the patients with rickets than in those without rickets. Since rickets seemed to be the result of renal loss of calcium combined with acidosis and impaired acidogenesis, it was decided to treat it with a low-sodium diet and with alkali in the form of sodium bicarbonate and sodium citrate. This treatment was effective without the use of vitamin D.

The subjective complaints subsided, the chemistry of the serum became normalized, and the deficiency in growth gradually disappeared. Addition of potassium salts to the diet did not prove necessary. The antirachitic effect of sodium citrate was greater than that of sodium bicarbonate. The following conditions develop as the result of ureterosigmoidostomy: (1) hyperchloremic acidosis, (2) potassium deficiency, and (3) calcium deficiency. The first 2 conditions can be explained without renal damage, but the last is probably due to renal loss of calcium as the result of defective acidogenesis, which in turn is caused by renal insufficiency as the result of urinary stasis and ascending infection. The absence of nephrocalcinosis remains unexplained. Another possible explanation is a renal loss of phosphorus induced by acidosis and resulting in a phosphorus-deficiency rickets. It is suggested that the metabolic complications of ureterosigmoidostomy could be prevented by an optimal surgical method and by a continuous prophylaxis with a diet low in chloride and high in sodium.

UROLOGY

Unilateral Renal Disease and Hypertension: Use of the Radioactive Diodrast Renogram as a Screening Test. C. C. Winter. J. Urol. 78:107-116 (Aug.) 1957 [Baltimore].

A renogram made with radioactive Diodrast was introduced as a new renal-function test for measuring individual renal vascular capacity, tubular cell function, and ability of the upper urinary tract to evacuate urine. Two sets of gamma-radiation detection and recording equipment (1 for each kidney) are used after an intravenous injection of Diodrast labeled with radioactive iodine (I^{131}) in tracer doses (1 μc for each 5 kg. of body weight). Preliminary findings indicated that this test might be a simple, painless, and accurate method for screening groups of hypertensive patients to discover the few who have unilateral renal dysfunction as the cause of their disease. While patients with abnormal renograms would then need extensive urologic examinations, those with normal renograms might be spared the discomfort and expense of such additional tests in most instances. The authors evaluated the renal status of 44 hypertensive patients by one or more standard renal function tests and the renogram with radioactive Diodrast. Excellent agreement was shown to exist. In 10 patients the renogram gave information indicating unilateral renal disease. This information plus that gained from conventional studies led to surgical treatment in 7 patients. In 9 of the 44 patients the renograms were normal on both sides and the standard renal function tests revealed no evidence of renal disease. In the remaining 25 patients both renograms were abnormal and one or more of the standard renal function tests also indicated bilateral disease.

The authors suggest the following plan for investigating hypertensive patients: 1. The history should be thoroughly investigated, and special examinations should be carried out to rule out acute and chronic glomerulonephritis, coarctation of the aorta, pheochromocytoma, periarteritis nodosa, and pituitary-adrenal disease. 2. A renogram should be made with radioactive Diodrast. 3. If this renogram reveals unilateral abnormality, a urologic investigation and aortography is generally indicated. 4. When surgical treatment is considered, individual renal clearance tests may be performed and their results compared with the renogram. On the basis of the data obtained in the 44 patients the authors conclude that the renogram with radioactive Diodrast is a rapid screening procedure for detecting unilateral renal disorders in hypertensive patients. The renogram proved to be a highly reliable method for detecting disorders of the individual kidney. However, this study is not sufficiently comprehensive to permit exact evaluation of its reliability in detecting all causes of renal hypertension. These preliminary results encouraged the authors to continue and enlarge the scope of this medical-urologic investigation of renal hypertension, particularly in children and young adults. This study also demonstrated the need for the combined efforts of the internist and the urologist to ensure an accurate diagnosis and effective therapy in these patients.

Physiology of the Human Solitary Kidney. N. S. R. Maluf, R. V. Ford and C. S. Spurr. J. Urol. 78:117-131 (Aug.) 1957 [Baltimore].

The studies described were undertaken to evaluate glomerular and tubular function of the healthy, congenitally solitary kidney in young adults and to measure effective renal blood-flow through such kidneys. The authors investigated the renal dynamics in 2 young men with healthy, congenitally solitary kidneys, in 1 young man with unilateral congenital renal hypoplasia and contralateral renal enlargement, and in 7 men with surgically solitary kidneys. This is the first such study of the congenitally solitary kidneys as far as the authors know. It was found that the renal dynamics of both the congenitally and surgically solitary kidneys are essentially equal. This reinforces previous anatomic studies that found the congenital and acquired solitary kidneys structurally identical. Previous workers have shown that the number of nephrons in a hypertrophied solitary kidney is essentially the same as in a single kidney of a normal pair. The tubular excretion of *p*-aminohippurate per minute of the healthy solitary kidney actually exceeds that of 2 normal kidneys. The effective renal plasma flow of the healthy kidney approximates that of 2 normal kidneys. The glomerular filtration rate of the normal kidney falls short of that of 2 normal kidneys. The internal diameter of the renal artery of a healthy solitary kidney is slightly (about 12.5%) but significantly greater than that of a normal kidney. Since volume-flow of a liquid through a tube varies to the 4th power of the radius of the tube, other things being equal, this small increase in arterial caliber is enough to allow for the doubling in volume-flow of blood which exists in the artery of a healthy solitary kidney.

Paratesticular Interstitial Cell Tumor in a Boy Aged Eleven. W. A. Barrett. J. Urol. 78:158-168 (Aug.) 1957 [Baltimore].

An 11-year-old boy was referred by his school physician because of his unusual development and because he had 3 testes. When he was 4 years old, his parents had noticed enlargement of the penis and growth of pubic hair. Some months later there had been considerable increase in weight with what appeared to be edematous tissue, and this was ascribed to a kidney condition. The penis gradually increased to adult size, the voice became deep and

resonant, and the muscular development was rapid. When he was 7½ years old, his facial hair became quite prominent as did the hair on the rest of his body. At 9 years of age he began to shave, and also at about this time he noted a swelling about the size of a walnut in the left scrotal sac. This was the tumor that the school physician had thought to be a third testis. Frequent erections and repeated emissions of seminal fluid were admitted. When the boy was examined at 11 years of age, he had the general appearance of a 20-year-old youth, his height was 61.75 in. (155 cm.), and his weight 130 lb. (59 kg.). The muscular development was that of an adult. The penis was of adult size and both testes were normally placed. An ovoid mass was found in the left scrotal sac. At operation this tumor mass was found within the tunica vaginalis, completely separate from the testis and slightly above it. The blood supply to this mass was separate and greater than that which supplied the testis and epididymis. The patient was observed at intervals of 3 to 6 months after operation, and his general appearance remained unchanged. Metastases, the only positive evidence of malignancy, have not thus far developed.

Leydig's interstitial cells produce the androgen excretion responsible for the male characteristics, such as enlargement of the penis, male distribution of facial and body hair, and deepening of the voice. The same testosterone also induces the enlargement and secretory action of prostate and seminal vesicles and is a factor in the closure of the epiphysial lines, with the resultant stunting of growth in these patients, and the marked muscular development. The case presented is the second reported in which the interstitial cell tumor was outside of the testis. These tumors are readily confused with arrhenoblastoma, adrenocortical rest, and Sertoli cell tumor. When interstitial cell tumor is suspected, preoperative studies should be carried out on the excretion of estrogens, androgens, 17-ketosteroids, gonadotropins, and intermediary products.

Congenital Absence of the Penis: Case Report. J. R. Haller, L. B. Schumaker and T. D. Furness. J. Urol. **78**:155-157 (Aug.) 1957 [Baltimore].

Absence of the penis is a rare congenital abnormality. The authors add 1 case to the 21 previously reported. The infant weighed 3,187 Gm. (7 lbs. 11 oz.) at birth, was lethargic, and responded poorly to artificial respiration. He was placed in an incubator. Complete absence of the penis was noted. The scrotum and raphe were normal, and both testes were descended and of normal size. No urethral orifice could be found. Respiration remained short and gaspy. Liquid meconium and pea-sized masses of meconium were expelled from the rectum, but no urine was excreted from the anus. After 7½ hours the infant became cyanotic, respiration became irregular, and he died. Autopsy revealed that the bladder was not distended, contained no urine, and ended blindly. Besides agenesis of the penis and the urethra there was a congenital megacolon, hypertrophy of the right ventricle of the heart, hepatomegaly, and partial congenital atelectasis of both lungs. The kidney showed imperfect formation of the tubules, the glomeruli were not mature, and the tubules were devoid of urine.

OTOLARYNGOLOGY

Aerotitis Media. D. C. Schechter, A. M. A. Arch. Otolaryng. **66**:117-126 (Aug.) 1957 [Chicago].

Aerotitis media is a noninfectious syndrome caused by obstruction of the auditory tube and its consequent failure to ventilate the tympanic cavity during rapid changes in atmospheric pressure. It occurs in flight during quick descent; it may also take place during compression in those working under increased air pressure, as in caissons and submarines. The symptoms are aural pain, a mild conductive deafness of the low-tone type, fulness in the affected ear, autophony, tinnitus, and, occasionally, vertigo. The diagnosis is made from the history, otoscopy, and nasopharyngoscopy. Animal experimentation has disclosed that the pathological changes in aerotitis are vascular. The extreme negative pressure or vacuum inside the occluded tympanic cavity draws the structures of the drum inward to such an extent that there is a degree of separation of the mucosal and fibrous layers, with subsequent edema and hemorrhage between the structures. The vacuum of the cavity sucks serosanguineous fluid from the lining mucosa. The prognosis is fairly good. Preventive measures consist in yawning, swallowing, jutting out of the jaw, and a grinding movement of the lower jaw. In the majority of cases of acute aerotitis media symptoms are mild, pain subsides early, and either no treatment or a minimum of conservative therapy is necessary. Resumption of flying should be avoided until otoscopic findings reveal complete recovery. The treatment of aerotitis media also includes correction of all nasopharyngeal and dental pathological processes.

Malignant Tumors of Rhinopharynx. A. Correa and A. P. Morgante. Rev. Hosp. clîn. **12**:255-260 (July-Aug.) 1957 (In Portuguese) [São Paulo, Brazil].

Malignant tumors of the rhinopharynx are rare. Thirty patients with this disease were observed in the department of otorhinolaryngology of the faculty of medicine of the São Paulo University. Most of the patients were between the ages of 20 and 40 years. There were 4 children between the ages of 2½ and 10 years. The histopathological type of the tumor was sarcoma in 10 patients, carcinoma

in 12, lymphoepithelioma in 4, and a malignant undifferentiated tumor in 1. A histological study of the tumor was not made in 3 cases. Twenty-one patients complained at the first consultation about 1 or more nodules in the neck, which proved to be metastases into the cervical lymph nodes. Other symptoms which appeared either before or after the cervical metastases were the following: nasal obstruction, hypoacusia, headache, ear-noises, earache, hemifacial neuralgia, dysphagia, bleeding from the nose, rhinorrhea, dizziness, disorders of the speech or of vision, nodules in the breast, and facial paralysis. The patients with cervical tumors were suspected of having a tumor in the rhinopharynx, the pharynx, or the larynx, unless the contrary was proved. Often the biopsy of a cervical metastasis suggested the presence of a rhinopharyngeal malignant tumor. For purposes of diagnosis a biopsy during posterior rhinoscopy was performed. The tumor remained invisible on posterior rhinoscopy for 6 to 12 months in some cases. Several biopsies were taken in such cases. Tomography and roentgen examination of the rhinopharynx, the paranasal sinuses, and the base of the cranium were of the greatest importance. The radiographies were taken in the classic panoramic anteroposterior position for the nasopharynx and in the submental-vertical position for the base of the cranium. The treatment consisted of roentgen therapy alone in 18 patients, roentgen therapy plus surgery in 3 patients, and roentgen therapy plus nitrogen mustard, chemicals, or radium therapy in 6 patients. Three patients refused any treatment. Only 5 patients reported for follow-up observations for more than 1½ years. Lymphoepithelioma remained healed for 18 months after discontinuation of treatment in 1 patient. Another patient with lymphoepithelioma survived 3 years after discontinuation of the treatment, with lesions in evolution. One patient with lymphosarcoma survived 5 years after discontinuation of treatment, with lesions in evolution. One patient with reticulohistocytoma and another with fibrosarcoma survived without recurrence of lesions for 5 and 1½ years respectively.

THERAPEUTICS

Studies on Synergism with Twelve Antibiotics Against Thirty Hospital Strains of Staphylococcus Aureus. H. J. Elliott and W. H. Hall. J. Lab. & Clin. Med. **50**:242-249 (Aug.) 1957 [St. Louis].

The combined antibacterial activity of 12 antibiotics, both singly and in 66 paired combinations, upon 30 hospital strains of Micrococcus (Staphylococcus) pyogenes var. aureus was measured by tube dilution with subcultures as well as by agar diffusion from paper strips with replica plating. There was a high incidence of strains resistant to penicillin, streptomycin, and the tetracyclines. Cross resistance was common to these antibiotics. Bacteriostasis was achieved at the lowest average concentration by novobiocin, vancomycin, and erythromycin. The most active bactericidal antibiotics were vancomycin, neomycin, and bacitracin. The combined activity of any 2 antibiotics was not enhanced if the strain of the micrococci was highly resistant to one or both antibiotics. Synergism was, therefore, infrequent between penicillin, streptomycin, and the tetracycline group. Resistance to the other antibiotics was not frequent. The most frequent enhancement of antibacterial activity in pairs occurred with the newer antibiotics, to which the hospital strains of the micrococci were most susceptible. These combinations include novobiocin with vancomycin, bacitracin with chloramphenicol, and erythromycin with cycloserine.

Experiences in Human Beings with an Improved Fat Emulsion for Intravenous Administration. J. F. Mueller. J. Lab. & Clin. Med. **50**:257-277 (Aug.) 1957 [St. Louis].

The results of the use of an improved fat emulsion for intravenous administration in 151 patients are compared with those of an emulsion of similar composition in 110 patients. The emulsions differed only in the purification of the soybean phosphatide emulsifier. Fever accounted for 88% of the total number of reactions in patients treated with the new emulsion as compared with 57% in patients treated with the old one. Reactions other than fever have been drastically reduced. Only 3 of 362 infusions could not be completed with the improved emulsion as compared with 23 of 293 infusions with the old emulsion. The old emulsion caused a flush in 6% of the patients, whereas only 1 patient had flushing with the new preparation. Nausea and vomiting occurred in 2.6% of the patients treated with the new preparation as compared with 13% of the patients receiving the old one. Significant blood pressure changes were observed in 13% of the patients when the old emulsion was administered. The rise in blood pressure seemed to be most closely related to the rate of infusion and could, with the new preparation, almost always be lowered by decreasing of the flow. Dyspnea and cyanosis occurred in 13% of the patients with the old infusion. None of the patients who received the new preparation were thus affected. Shock was seen in 2 patients receiving the old emulsion, occurring within the first 3 minutes of the infusion; both patients survived without any obvious sequelae. No such reaction was encountered with the emulsion presently employed. Rash was observed in 1 child receiving the new emulsion. Two reactions were observed with the new preparation, which continued after its withdrawal. One reaction occurred in a patient with cirrhosis of the liver and consisted of a backache associated with gross tremor of the

hands and head; this reaction was clouded by an overtone of hysteria. The other occurred in an 89-year-old man with generalized arteriosclerosis and arteriosclerotic heart disease. Semistupor, accentuated by Cheyne-Stoke's respiration, supervened. These signs disappeared several hours following the withdrawal of the fat emulsion. No mortality and no permanent disability from any acute morbidity was seen in the total of 655 infusions.

The fact that out of a total of 362 infusions only 3 could not be completed attests to its practicability and safety. The addition of supplemental protein to the emulsion is, however, still desirable. The present formula will not permit supplementation with amino acids, since this will break the emulsion, as does the addition of electrolytes.

Adrenal Cortical Steroid Treatment of Grave Intoxications and Shock. T. Andersen and M. Iversen. Ugesk. læger **119**:997-1002 (Aug. 1) 1957 (In Danish) [Copenhagen].

The 1st of 4 cases of gravely affected general condition with severe intoxication or shock occurred in a girl, aged 3, with acute capillary bronchitis; the 2nd in a girl, aged 3, with suspected fulminant meningococcic sepsis; the 3rd in a boy, aged 16 months, with persisting shock and in diabetic coma, and the 4th in a girl, aged 10, with measles-encephalitis. In all cases decisive improvement in the general condition occurred within 12 hours after administration of hydrocortisone intravenously. That the infection itself is not influenced by the hydrocortisone is clearly illustrated in the 1st case, and the importance of simultaneous adequate treatment with antibiotics is stressed. Lines of guidance are given for treatment in manifest adrenal insufficiency, including Addisonian crisis, and in prophylaxis, especially for patients undergoing surgery who have previously been treated with steroids or are under treatment with steroids.

Change in the Sensibility to Various Antibiotics of Strains of Staphylococcus Aureus Isolated During the Year 1956. A. D'Agata. Riforma med. **71**:840-841 (July 27) 1957 (In Italian) [Naples].

The resistance of some strains of Micrococcus (Staphylococcus) pyogenes var. aureus isolated from human material of hospitalized patients was studied. Findings revealed that 86.1% of the strains were resistant to penicillin, 25% to streptomycin, 22.2% to chloramphenicol, 27.8% to chlortetracycline (Aureomycin), 16.8% to oxytetracycline (Terramycin), and 8.4% to erythromycin. These findings, compared with those of similar studies carried out in the same hospital in 1954, showed that there has been a decrease in the strains resistant to streptomycin, chloramphenicol, chlortetracycline, and oxytetracycline and a slight increase in the strains resistant to penicillin and to erythromycin.

The Combined Use of Isoniazid and Nupasal-213 in Pulmonary Tuberculosis: A Study of the Toxic Effects and the Development of Cross-Resistance Between Isoniazid and Nupasal-213 in the Treatment of Pulmonary Tuberculosis. J. Cuthbert and L. G. Bruce. Brit. J. Tuberc. **51**:265-270 (July) 1957 [London].

Nupasal-213 and Salizid are trade names of *o*-hydroxybenzal isonicotinylhydrazine, which is a yellow crystalline substance formed by the interaction of isonicotinic acid hydrazide and salicylaldehyde and purified by repeated recrystallisation from ethyl alcohol. On a gravimetric basis it contains slightly over 50% isoniazid nucleus. The investigations presented here were concerned with (1) a therapeutic trial, (2) an in vitro test for cross resistance, and (3) an animal (guinea pig) test for cross resistance. In the therapeutic trial the drugs were given to a test group in a dose of 200 mg. of isoniazid plus 1,600 mg. of Nupasal-213 daily. Two tablets, each containing 50 mg. isoniazid and 400 mg. Nupasal-213, were given twice daily. The object of this part of the investigation was to see if the combination of the drugs would prevent the emergence of tubercle bacilli resistant to either drug and to see if any toxic effects were manifested by the combined use of these closely related drugs, each given in their usual dose. To a control group were given 10 Gm. aminosalicylic acid and 200 mg. isoniazid daily. The patients chosen for study were those who had had chronic cavitary pulmonary tuberculosis of at least a year's standing, in whom there was not much likelihood of radiological improvement or sputum conversion with intensive drug therapy, and in whom surgical intervention was not possible. The subjects were over 18 years of age, and most had had various courses of treatment with combinations of streptomycin, aminosalicylic acid, and isoniazid in the past. As suitable patients appeared at the clinic for routine review they were placed alternately in the test and control group.

It was found that neither drug can guard against the tubercle bacilli becoming resistant to the other. Patients in the control group treated with isoniazid, streptomycin, and aminosalicylic acid developed resistance to isoniazid much less readily than the patients in the therapeutic trial, and it is concluded that treatment on these accepted lines is the treatment of choice for patients with chronic, sputum-positive pulmonary tuberculosis with sensitive organisms. Patients treated with a combination of isoniazid and Nupasal-213 in the dosage used showed a high incidence of neurotoxic symptoms. Experiments with guinea pigs showed that neither

Nupasal nor a combination of Nupasal and isoniazid will keep alive or cure an animal infected with virulent isoniazid-resistant organisms. Isoniazid-resistant tubercle bacilli grew readily on mediums containing Nupasal-213 in full strength. As far as clinical use is concerned Nupasal-213 (Salizid) and isoniazid are identical. They should not be used alone or together without the addition of antituberculosis drugs of different chemical structure.

The Value of Chloroquine in Rheumatoid Disease: A Four-Year Study of Continuous Therapy. A. Bagnall. Canad. M. A. J. **77**:182-194 (Aug. 1) 1957 [Toronto].

A 4-year study of continuous daily treatment with orally administered chloroquine (Aralen) phosphate in 125 patients with rheumatoid diseases is reported. The results were considered good in 70% of the patients. The major objective gain in these patients was improved work performance, sedimentation rate, and hemoglobin levels. Most of the patients (90%) remained on chloroquine therapy, half of them for more than 2 years. Patients with peripheral rheumatoid arthritis, spondylitis, arthritis of juvenile onset, and rheumatoid disease with psoriasis responded equally well to the drug. Thirty per cent of the patients had subjectively improved, although their treatment was considered a failure. All patients were given 1 tablet containing 0.25 Gm. of chloroquine daily. A lesser dosage was found necessary in 36% of the patients to avoid toxic reactions. Permanent withdrawal was required in 10% for this reason. No definite severe toxic effects were encountered, but minor toxic reactions were more frequent than expected. Drug dermatitis was the only reaction in 16% of the patients; dosage and treatment had to be restricted. Leukopenia occurred 6 times in this series, the white blood cell count rising after some weeks to normal despite continued full-dosage chloroquine therapy. Short courses of chloroquine therapy are of no value, since the drug begins to show its favorable effects after 1 to 3 months. Maximum benefit may be delayed for 6 to 12 months in patients with severe arthritis. Chloroquine appeared to come closer to the ideal for long-term, safe control of rheumatoid disease than other now available agents. Little is known of its mechanism of action.

Mecamylamine and Its Mode of Action. G. Bennett, C. Tyler and E. Zaimis. Lancet **2**:218-222 (Aug. 3) 1957 [London].

The search for a better ganglion-blocking agent led to the discovery of mecamylamine (Inversine), whose formula is 3-methylaminoisocamphane hydrochloride. Unlike hexamethonium and pentolinium, mecamylamine is a secondary amine and as such is easily absorbed from the gastrointestinal tract. The combination of good absorption from the gastrointestinal tract and long action was considered advantageous by clinicians, and the drug was immediately used in the treatment of hypertension. Such a long action, however, together with the fact that mecamylamine has a molecule chemically different from those of hexamethonium and pentolinium, raised a doubt as to whether its mode of action could be the same as that of hexamethonium and pentolinium. The authors discuss the action of mecamylamine on autonomic ganglions and on the neuromuscular junction. They found that the mode of action of mecamylamine is completely different from that of hexamethonium and pentolinium. Mecamylamine is a substance readily diffusing into cells, and its effects at the autonomic ganglions and neuromuscular junction are not produced by a competition with acetylcholine. Apparently the compound alters the physiological state of the ganglion cell and of the muscle fiber, an alteration leading to a modified response of these structures to acetylcholine, acetylcholine-like drugs, or drugs competing with acetylcholine. The effects produced by mecamylamine are not restricted to the autonomic ganglions and neuromuscular junction. The compound acts on the central nervous system and has a direct effect on the intestine and heart.

That clinical manifestations are due not only to a ganglion blockade is also suggested by the slow onset of the hypotensive action of mecamylamine in humans. Even after intravenous administration, the onset of hypotension may be delayed for 30 to 60 minutes. The authors suggest that the fall in blood pressure which mecamylamine produces results from actions at several sites. Drugs mimicking or competing with acetylcholine should be given only with great caution in the presence of mecamylamine.

A Comparison of Cortisone and Prednisone in Treatment of Rheumatoid Arthritis: A Report by the Joint Committee of the Medical Research Council and Nuffield Foundation. Brit. M. J. **2**:199-202 (July 27) 1957 [London].

Sixty-eight patients with rheumatoid arthritis who had been taking cortisone acetate for one year or more were divided into 2 equivalent groups. One group continued to take cortisone; the other was transferred to prednisone acetate therapy. At the end of the year the cortisone group showed no improvement, and there was evidence of deterioration in the slightly increasing number of patients assessed as having very active disease. The prednisone group showed improvement in the strength of grip, blood sedimentation rate, hemoglobin level, general functional capacity, and disease activity. This group showed a definite improvement after 4 weeks of treatment. The number with only slight disease activity increased from 19 to 27, and, further, 3 were in complete remission. This improvement was maintained at 12 weeks, but thereafter

there were clear signs of a falling back. At the end of the year the number of patients in remission had increased to 5, the number with only slight activity had fallen to 18, and the number with moderate activity had risen to 11, compared with 15 originally and only 4 at the 12th week. Four of the 35 prednisone patients were capable of full activity on entry to the trial, 9 after 4 weeks' treatment, and 8 at the end of the year.

The partial loss of improvement may have been partly due to a reduction of prednisone dosage during the year. The dosage was adjusted to obtain maximum benefit without side-effects, but side-effects were noted. Patients in the cortisone group showed no change in the incidence of side-effects, while for prednisone patients the most marked change was the increased incidence of moonface, from 11 cases at the beginning of treatment to 19 at the 12th week and 20 at the end of the year. There was also some increase in the number of patients with dyspepsia, and, in the first month only, with euphoria. The authors believe that the more favorable results observed with prednisone may be due, in part, to the use of a dosage relatively high in comparison with that given in the form of cortisone.

Prolonged Antibiotic Treatment of Severe Bronchiectasis: A Report by a Subcommittee of the Antibiotics Clinical Trials (Non-tuberculous) Committee of the Medical Research Council. Brit. M. J. 2:255-259 (Aug. 3) 1957 [London].

The effect of prolonged antibiotic therapy in 112 patients with severe bronchiectasis characterized by abundant purulent or mucopurulent sputum was studied. The patients were treated entirely at home and were attended regularly at a special outpatient clinic over a consecutive period of 52 weeks. The drugs were provided in indistinguishable 0.25-Gm. capsules, 2 of which were given 4 times a day on 2 days each week. Of the 112 patients, 36 were given penicillin, 40, oxytetracycline, and 36, lactose. The responses to the treatments were compared at the end of the year. The physicians' assessment recorded 42% of the patients treated with penicillin, 60% of those treated with oxytetracycline, and 28% of those given lactose as improved, although much of the improvement was attributed to regular postural drainage. Each group showed a reduction in sputum volume, greater for the pus than for the mucus fraction. The reduction in the group given oxytetracycline was rapid and about one half the pretreatment level. The reduction in the groups given penicillin and lactose was about 70% of the original level in each. The severity of cough and dyspnea was reduced in each treatment group. A slight advantage was shown by the oxytetracycline group in the reduction of episodes of hemoptysis. Only 2 patients, both given penicillin, were worse at the end of the year. Three patients died, one in each group. No serious toxic effects were observed in any group. The oxytetracycline regimen used is both beneficial and safe in patients with severe bronchiectasis. It is, however, expensive, and the response obtained and expense entailed do not justify the widespread use of long-term oxytetracycline therapy in most patients with bronchiectasis. For the relatively few advanced cases it does offer a measure of relief not apparently attainable by orally given penicillin in the doses used. The characteristic symptoms of bronchiectasis can be modified as long as oxytetracycline therapy is maintained, but there is no indication that such improvement as may be achieved is permanent, and relapse is almost certain after treatment is discontinued.

Adult Chronic Bronchitis—the Infective Factor and Its Treatment. G. Edwards, A. R. Buckley, E. C. Fear and others. Brit. M. J. 2:259-264 (Aug. 3) 1957 [London].

The results of an investigation into certain bacteriological aspects of the infective factor in chronic bronchitis and of a controlled therapeutic trial with oxytetracycline alone or combined with a sulfonamide and with an autogenous hemophilus influenzae vaccine in 53 patients with chronic bronchitis are reported on. The 8 treatment groups were reasonably well balanced for age, sex, duration of symptoms, purulence and volume of sputum, and degree of disability. Most patients taking active drugs were maintained after the first month's treatment on 0.5 Gm. or less of oxytetracycline and/or sulfonamide given twice daily. Toxic effects from this dosage were not a serious problem, and it was not necessary to withdraw any patient from the trial. The mean percentage level of improvement of the whole series was found to be 37%. The results following oxytetracycline therapy were better than those achieved with a sulfonamide. The autogenous vaccine had little, if any, clinical effect. The authors agree with most other workers that H. influenzae and the Pneumococcus are the predominant potential pathogens found in chronic bronchitis. The incidence of H. influenzae is twice as great in purulent as in mucoid sputum, whereas that of the Pneumococcus is unrelated to sputum purulence. No significant change could be detected in the flora of bronchitic sputums after clinically effective antibacterial drug treatment.

Sickle-Cell Disease: New Method of Treatment, Preliminary Report. G. Hilkovitz. Brit. M. J. 2:266-269 (Aug. 3) 1957 [London].

There is no effective treatment for sickle-cell disease at present, and it is suggested that acetazolamide may be employed to control the occurrence of sickling. Evidence has been produced to

show that acetazolamide inhibits the occurrence of sickling of red blood cells in vitro and in vivo. An 8-month-old Negro baby with sickle-cell disease was given acetazolamide. In the period of 41 days preceding the administration of the drug, there was evidence of active hemolysis. The patient had, at the time of writing, been treated with acetazolamide for 29 days. A steady rise in the hemoglobin levels from 7.1 to 9.4 Gm. per 100 ml. of blood was observed during this period. The child, under observation for 70 days, continued to gain weight and became more alert and active than before treatment was started. Natural remissions occur in the disease, and no conclusions can be drawn from this remission. A therapeutic trial was in progress at the time of writing.

PUBLIC HEALTH

Cost of Administration of Salk Vaccine Program. J. M. Bistowish and W. T. Weathington. J. Florida M. A. **44**:150-152 (Aug.) 1957 [Jacksonville].

The Federal Polio Act of 1955 allotted $780,000 to Florida for a program of vaccination against poliomyelitis. According to the plan, Florida was allowed to use $564,000 of this amount for the purchase of vaccine and $216,000 for its administration. It was decided that in this state, 3 jurisdictions, as nearly as possible representative of the state as a whole, would be selected to make the validation time and cost studies. The following tentative conclusions are derived from an incomplete time-cost study: 1. The probable cost to administer 404,470 doses of poliomyelitis vaccine to Florida's children was $159,600, or $0.395 per dose. This figure does not include the cost of the vaccine or fees paid to private physicians by individuals. 2. The cost of a county program of distribution of vaccine to private physicians with the necessary collection of reports and other supportive activities was essentially the same as for a county program in which practically all immunizations were given by the health department. 3. The cost of the immunization program in the rural counties was more than twice the cost found for either urban county. This is additional proof that the cost of rural public health is high. It is realized that a study of this sort is subject to a great many sources of error. The counties selected as the sample may not be typical or representative of the state as a whole. There could also be great variability in the daily accounting of time by the individual workers. It is believed, however, that the study was sufficiently well controlled to determine roughly the cost of administering the vaccine. It should also be emphasized that this is an interim report and that the costs found at this time may not be the same as those computed when the study is completed.

PATHOLOGY

A summary of the Newer Knowledge of Toxoplasmosis. W. H. Wright. Am. J. Clin. Path. **28**:1-17 (July) 1957 [Baltimore].

Research in toxoplasmosis has been conducted in the author's laboratory for the past 8 years, and much of the data presented relate to these studies and the impressions derived from them. Although not many cases of human toxoplasmosis have been reported, they have had widespread distribution, having been recognized in numerous places in the Western Hemisphere and in Europe and less frequently in other parts of the world. Infection in lower animals is even more widespread. The occurrence of antibodies in various population groups indicates that man is frequently exposed to infection with Toxoplasma gondii. The percentage of positive reactors usually increases with age. The infection is more prevalent in warm, moist areas than in cold or hot, dry climates. It is not yet possible to analyze the significance of such data. Because infection is frequent in domesticated animals, it has been assumed that these animals serve as reservoir-hosts and that man acquires his infection from them. It has also been assumed that infection may be acquired through the oral route or that it may be transmitted by insects. Exposure through the contaminative route would seem unlikely, owing to the low resistance of the organism to environmental factors. Equivocal results have been obtained in experiments in which animals have been fed meat that contained the proliferative forms of the parasite, but more consistent findings have resulted from the feeding of material that contained the pseudocysts, which are more resistant than the proliferative forms.

In spite of a large amount of experimental work, transmission by insects has not been proved, although certain of the results would seem to warrant further investigation. Toxoplasmosis may be classified as congenital and acquired. Acquired toxoplasmosis has been categorized in accordance with its varying clinical manifestations into exanthematic, cerebrospinal, ophthalmic, and lymphadenopathic forms. Clinical diagnosis of acquired toxoplasmosis is difficult, if not impossible, and must be augmented by laboratory procedures, such as serologic tests (especially the dye test) and the inoculation of animals. Of the large number of drugs that have been tested in animals, the combination of pyrimethamine and the sulfonamides has yielded the best results. On the other hand, pyrimethamine may produce disagreeable reactions and, in large or continued dosage, may be responsible for various hematological changes, including a megaloblastic type of anemia.

BOOK REVIEWS

Injuries of the Hand. By Ronald Furlong, F.R.C.S., Assistant Orthopaedic Surgeon, St. Thomas's Hospital, London. Cloth. $9. Pp. 215, with 99 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6; J. & A. Churchill, Ltd., 104 Gloucester Pl., Portman Sq., London, W. 1, England, 1957.

This book should serve as an excellent source of information to those dealing with any form of hand injury from simple laceration to multiple tissue injury. The initial chapters deal with surgical anatomy and general principles of hand surgery. No mention is made of the braided wire, barbed, withdrawable suture that has found enthusiastic supporters in the United States. The technique described is that of Brummell. All types of injuries are discussed, including skin loss, tendon laceration and loss, nerve laceration, and fractures. Beyond the realm of hand injury are chapters dealing with hand infections and tenosynovitis. Preservation of tissue is justly emphasized throughout. The chapter on fractures and dislocation presents views on treatment that are at variance with those of many surgeons. Skeletal digital traction for Bennett's fracture is not considered as barbarous by many as open reduction with internal fixation. The book contains many excellent diagrams, clinical photographs, and roentgenograms that add much to the value of this book. This volume is highly recommended to those who treat hand injuries, both residents and practitioners.

Medical Ethics: A Guide to Students and Practitioners. Edited by Maurice Davidson, M.A., D.M., B.Ch., Consulting Physician to Brompton Hospital, London. Cloth. 20 shillings. Pp. 165, with 1 illustration. Lloyd-Luke (Medical Books), Ltd., 49 Newman St., London, W. 1, England, 1957.

This book includes 12 essays and papers on the application of ethical principles to the everyday occurrences that arise in the practice of medicine. Subjects range from a practical discussion of the structure and function of the general medical council to a discussion of experimental medicine. Particularly interesting are the papers on the care of the dying, the doctor's responsibility to his family, and the doctor-patient relationship. The essays on the doctor, the law, and the police and the doctor's relationship to his professional colleagues are less a discussion of ethical principles than of etiquette and the law, but they are nonetheless enlightening and germane to the central theme of the work.

While it is true that several books on medical ethics have appeared recently, and while this one reflects the thinking and practice common to the British Isles, it is, nevertheless, because of its practical approach to everyday situations, a contribution of value to physicians. It does not duplicate the material or discussions that have appeared in other books, and it is not in any sense provincial. The universality of ethical principles and the common goal of physicians the world over are accentuated by this collection of essays. On such controversial issues as artificial insemination the essayist not only presents his own view but also presents the contrary point of view fairly and objectively. Most physicians should find this work satisfying. It is practical and constructive. It is not forbiddingly heavy. Being a collection of essays, it need not be read all at once, and it would be safe to assume that some of the chapters will be read and reread.

Anesthesia and Otolaryngology. By Donald F. Proctor, M.D., Assistant Professor of Laryngology and Otology, Johns Hopkins University School of Medicine, Baltimore. Cloth. $7. Pp. 267, with 33 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1957.

It has become extremely difficult to prepare a single-volume textbook on anesthesiology that covers comprehensively the entire field of the practices of the specialty. Recently authors have surmounted this difficulty by confining the subject matter to a single phase of the subject. Hence a number of monographs have appeared covering a specific small area. This is such a monograph. The author's purpose in preparing this volume was to present his views regarding the problems common to the anesthesiologist and the otolaryngologist. The book is divided into four sections. The first deals with mortality and mobidity. Statistical data are presented and some of the major or at least the dramatic complications, such as cardiac arrest, are discussed from the standpoint of management. This approach is used throughout the text. The problems are presented simply, with a practical outline of their prevention and treatment. Another chapter in the first section discusses preanesthetic preparation. The approach to the patient through his history, examination, and psychological considerations receives attention as well as the use of drugs. Unfortunately, the author omitted any discussion of tranquilizers. There is a short consideration of medico-legal problems, which is undoubtedly included for completeness, since the problem is not one that in-

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

volves only the otolaryngologist. Other parts of the book have the same purpose; for example, the last chapter is entitled, Respiratory Resuscitation in the Newborn.

The author is conservative in his approach in the second section to the subject of general anesthesia for otolaryngeal procedures. The recommended drugs and techniques are those of proved merit. Emphasis is given such important considerations as pulmonary ventilation, postanesthetic care, and complications that are anticipated during and after operation. In the third section procedures of local anesthesia are discussed. The choice of drugs is introduced first and considered briefly. Only four are mentioned, and the discussion of these and other factors in local anesthesia, such as preanesthetic use of barbiturates, hyaluronidase, toxicity, and vasoconstrictors, occupies only 11 pages. The remainder of the third section is given to local-anesthetic management of specific operations. The author draws on his personal experiences for emphasis. In the final section, probably the most useful, respiratory obstruction is well described. There is a good bibliography at the conclusion of each chapter and an adequate index. The illustrations are simple but effective. The book is attractively printed with readable type. This volume should be popular with anesthesiologists and otolaryngologists, particularly those who are in the preparatory years of their specialties. It will not be so useful to the medical student. It is recommended as a conservative, practical, and authoritative manual.

Medical Writing: The Technic and the Art. By Morris Fishbein, M.D. Third edition. Cloth. $7. Pp. 262, with 36 illustrations. Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36; 95 Farringdon St., London, E.C.4, England; 253 Spadina Rd., Toronto 4, Canada, 1957.

This standard work on the preparation of medical manuscripts deserves its well-earned place in the literature on the subject. It has been out of print and has been missed. It is a manual of style rather than a textbook on medical writing, since it sets forth standards for abbreviation, footnotes, bibliographic material, charts, illustrations, etc., which are based largely on the standards of THE JOURNAL. As a manual of style it successfully fills a need. It complements, but does not replace, other books on medical writing which provide better discussion of such subjects as exposition, sentence and paragraph structure, elementary biometrics, and grammar. Both types of book are highly desirable, if not essential, for the serious student of medical writing. This new edition has been changed very little from the last. It has been brought up to date in all necessary areas, although the changes are of greater importance to an editor than to an author. Authors, and editors should find the book valuable for reference.

The Surgical Management of Pulmonary Tuberculosis. Edited by John D. Steele, M.D. Introduction by Frederick A. Coller, M.D. Biographical sketch of John Alexander by Cameron Haight, M.D. Publication number 1, John Alexander monograph series on various phases of thoracic surgery. Cloth. $9.50. Pp. 213, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1957.

This is the first of a series of monographs on thoracic surgery written by thoracic surgeons who were trained by the late John Alexander. In addition to Dr. Alexander's contributions to the development of thoracic surgery, his greatest contribution was his training of young men. The present excellent monograph is evidence of this. Great physicians are often great teachers, and it is proper and customary that the students of such a teacher as Dr. Alexander should express their loyalty and their sense of indebtedness to him by the publication of a commemorative volume. This is an excellent handbook of modern practice and is doubly excellent because of its historical thoroughness and its large bibliography.

Fundamentals Of Human Physiology for Students in the Medical Sciences. By W. B. Youmans, Ph.D., M.D., Professor of Physiology, University of Wisconsin, Madison. Cloth. $8.50. Pp. 567, with 180 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1957.

A commendable effort is made in this book to present the essential facts of human physiology for medical students within 540 pages. The effort has been, on the whole, successful, partly because of a good selection of illustrations and partly because of the exclusion of the usual quota of historical and theoretical material. It is also assumed that medical students will find the necessary collateral anatomic and biochemical information in other courses and that applied or clinical aspects of physiology are adequately dealt with elsewhere. The three parts of the book, following an introductory chapter on general principles, are devoted to nerve, muscle, junctional transmission, reflex action, central nervous system, and senses; circulation and respiration; and nutrition, digestion, metabolism, endocrinology, and excretion.

A few disconcerting errors may be noted, but this book can be recommended to students and teachers of physiology in medical schools.

QUERIES AND MINOR NOTES

TRANSMISSION OF INFECTIOUS HEPATITIS

To the Editor:—*A 4-year-old boy was bitten by a dog; the wound was cauterized, and a tetanus toxoid booster injection given. About six to seven weeks later the child became acutely ill, being given a diagnosis of infectious mononucleosis associated with hepatitis. After a stormy course of seven weeks the patient improved with supportive treatment. About 10 months later his 9-year-old brother was bitten by a dog from the same neighborhood. The wound was treated with an antiseptic, and a tetanus toxoid booster injection given. About six to seven weeks after this bite the brother became ill with hepatitis. This child also improved in seven weeks with supportive treatment. What is the relationship between the above illnesses and the dog bites, and what are the probable etiological factors and sequelae?*

M.D., Connecticut.

Answer.—It can be categorically stated that no cases of hepatitis have been reported from dog bites. "Infectious hepatitis" of dogs is not due to the same virus which produces infectious hepatitis in humans. Infectious mononucleosis has also never been reported to be produced by dogs. If there is any causal relationship between the hepatitis and the dog bite, then one would have to assume that the hepatitis followed the tetanus injection, due to the use of a contaminated needle or syringe. If the diagnoses of infectious mononucleosis and of infectious hepatitis were correct, then there can be no connection between these two cases. It is possible, however, that the second child actually had mononucleosis or that both children had infectious hepatitis. In the latter case, the second child might have contracted the virus from the first, provided that the first child continued to be a fecal carrier for a 9-or-10-month period. Such cases have been demonstrated, but probably occur only when persistent or chronic disease is present. The sequelae of such cases as are described are the same as with the ordinary case of infectious hepatitis. Recovery is generally complete in children of this age. However, it is probable that a certain small percentage develop chronic liver disease, and a few cirrhosis of the liver of a progressive nature.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

AFIBRINOGENEMIA

To the Editor:—*Are there any data on the likelihood or incidence of afibrinogenemia occurring in missed abortion, where the patient is treated conservatively and spontaneous abortion awaited? If so, would this possibility offset the advantages of the alleged decreased morbidity in cases treated conservatively as compared with those treated by immediate dilation and curettage, once the diagnosis has been made?*

M.D., Massachusetts.

Answer.—In a two-year period Weiner and associates (*Am. J. Obst. & Gynec.* **60**:1015, 1950) studied 15 Rh-negative patients who had anti-Rh agglutinins with intrauterine death presumably on the basis of this isosensitization. In all cases the fetuses were retained in utero for various periods after death. In 3 of these 15 patients there were marked defects in the coagulation mechanism. The authors warned that, unless afibrinogenemia is recognized in such cases and promptly treated, serious hemorrhage may occur at the time of labor and delivery. Pritchard and Ratnoff (*Surg. Gynec. & Obst.* **101**:467, 1955) mention that in 23 patients in whom fetal death appeared to have taken place between the 12th and the 36th week of gestation, and the dead fetus had been retained in utero for 3 to 11 weeks, no evidence was found of a critical depletion of circulatory fibrinogen. In seven of these patients serial fibrinogen determinations were made for several weeks after intrauterine death. In all seven there was a progressive reduction in the concentration of circulating fibrinogen, but the concentration at no time reached a level lower than that in the normal nonpregnant woman. During the same period of time, eight cases of prolonged intrauterine retention of a dead fetus were encountered, in which the fibrinogen level was dangerously low. In three instances hemorrhagic manifestations prompted studies of the fibrinogen concentration in the patients' plasmas. In the remaining five cases the hypofibrinogenemia was discovered in a routine study of patients with intrauterine retention of a dead fetus. Hence, in the total of 31 cases of retained dead fetuses there were 8 instances of hypofibrinogenemia. However, as Pritchard and Ratnoff say, these data do not reflect the true incidence of abnormal hemostasis in this syndrome. Although the first cases of hypofibrinogenemia with death of the fetus were in Rh-negative women, it is estab-

lished that the process is not peculiar to such patients. Three of Pritchard and Ratnoff's patients were Rh-positive.

Since the exact incidence of hemorrhagic disturbances in cases of retained dead fetuses is not known, the management of missed abortion should be conservative, because early attempts to empty the uterus can be serious. However, beginning with the third week after apparent fetal death, the concentration of fibrinogen in the plasma should be determined weekly. There need be little fear in the early weeks, because hypofibrinogenemia has not been detected before the fifth week after fetal death. If the concentration of fibrinogen falls below 150 mg. per 100 ml., the uterus should be emptied promptly. At least 4 Gm. of human fibrinogen and several units of compatible whole blood should be immediately available.

Pritchard and Ratnoff say that labor and vaginal delivery, with or without Pitocin stimulation, will not result in any significant change in the concentration of circulating fibrinogen even if hypofibrinogenemia is present. If the induction of labor is judged not possible or if attempts at induction fail, abdominal hysterotomy should be carried out. In the cases in which induction of labor is successful, it is probably safest to give fibrinogen before the anticipated time of delivery. Following emptying of the uterus, close attention should be given to the blood loss from the vagina. An intravenous infusion of diluted Pitocin for several hours after hysterotomy is desirable to aid in the maintenance of a well-contracted myometrium. If bleeding does occur, clot observation tests should be performed to determine whether fibrinogen must be given. Present evidence indicates that, once a uterus is emptied, the process of defibrination ceases, and hemostasis can be maintained without further administration of fibrinogen.

POWDERED CHARCOAL

To the Editor:—*Powdered charcoal is recommended for bad breath. Are there any deleterious effects, particularly to the gastrointestinal tract, from taking this substance over a long period of time?*

Francis E. Guinney, M.D., Los Angeles.

Answer.—This consultant is unaware of any evidence indicating chronic deleterious effects from ingesting powdered charcoal in small amounts over long periods of time. The adsorptive properties of activated charcoal have promoted its trial in the treatment of many and varied disease conditions. In the intestinal tract, it has been reported that activated charcoal will remove many irritating substances, such as toxic amines and organic acids of decomposed foods, probably also the bacteria themselves (Dietzel: *Apoth. Ztg.* **47**:283, 1932). There is one report (Emery: *J. A. M. A.* **108**:202-205 [Jan. 16] 1937) that ingested activated charcoal may adsorb enzymes, vitamins, and minerals and hence interfere with digestion. It has been shown (Messerli: *Arch. internat. physiol.* **19**:103, 1922) that rats and pigeons, fed on a diet of decorticated rice, developed an avitaminosis more rapidly and more severely if blood charcoal were mixed in the diet; however, these observations were made only when large amounts of charcoal were given (100 Gm. or more). It would be the opinion of this consultant that the amount of charcoal one might ingest to help overcome bad breath would have no adverse physiological effect.

DIATHERMY TO HEART MUSCLES

To the Editor:—*Do the newer types of short wave diathermy machines or other high frequency heat therapy machines have sufficient penetrating power to reach the heart muscle? If so, would daily applications of such heat therapy over a long period of time help to relieve myocardial ischemia? Would it help to promote the development of collateral circulation if used over a long period of time? Finally, would the application of such heat therapy have any effect on atheromatous plaques in the coronary arteries; that is, would it soften them, probably finally causing dissolution?*

Philip Russillo, M.D., Jersey City, N. J.

Answer.—Shortwave and microwave diathermy apparatus available today may reasonably be expected to cause some heating of the intact heart. However, microwaves of the frequency 2450 megacycles are so well absorbed by body fluids that the use of this physical agent on the heart, a fluid-containing organ, may be considered as contraindicated. In the 1930's, a number of studies appeared in the European medical literature, and a few in the American medical literature, which claimed to show that the use of the conventional long-wave diathermy (now nonexistent in the United States) and shortwave diathermy would be of no value in the relief of angina pectoris. The procedure was not without its dangers however. It was rather difficult to evaluate the clinical results claimed because of the variable course the disease. In the absence of more recent, carefully controlled, and extensive studies, it does not seem justifiable to conclude that diathermy will be effective in the treatment of angina pectoris or in the development of collateral coronary circulation.

Diathermy would be definitely contraindicated in the early stages following acute coronary occlusion, because the use of diathermy is contraindicated in the early stages following trauma. The application of diathermy increases diffusion and bleeding in an injured area for varying periods after the

injury, so its use is contraindicated after acute myocardial infarction. Further, the application of heat of any kind to the subject with impaired cardiac function must be done most judiciously because of the added demands made upon the circulatory system. Thus, in view of the lack of evidence of the value of diathermy in the condition mentioned, the dangers in its application to the cardiac patient, and the demonstrated efficacy of drug therapy, these physical agents do not seem justified for local application to the heart.

STERILIZATION TO PREVENT TRANSMISSION OF HEPATITIS

To the Editor:—*Is boiling of needles for 10 minutes sufficient for the prevention of transmission of infectious hepatitis?*

J. M. Dell Jr., M.D., Gainesville, Fla.

Answer.—There is no evidence to substantiate that boiling needles and syringes for 10 minutes in water will destroy the virus of infectious hepatitis or of homologous serum hepatitis. Autoclaving for 10 to 15 minutes at 121 C (250 F) or sterilizing in a hot air oven at 165 C (329 F) for one hour is a far more reliable procedure. Prior to any sterilization procedure, residual blood and tissue should be eliminated by thorough mechanical cleansing of needles and syringes. In lieu of an autoclave, a pressure cooker containing water can easily be adapted as a sterilizer and used on a hot plate. A temperature of 115 C (240 F) will be attained by a pressure of 10 lb. per square inch (at sea level). A 30-minute cycle at that temperature will effect sterility. If lower pressures and temperatures are employed, the time interval must be increased.

HYPERSENSITIVITY TO LIGHT

To the Editor:—*A 51-year-old woman has developed an "allergy" to the sun. Even when the sunlight comes through glass windows, or on a hazy day, an urticarial rash, with edema and marked pruritus, will develop in a few seconds. Her face is least affected, but a usually unexposed area of skin, for instance, the upper arms because of shorter sleeves or the newly exposed neck line after a hair cut, is affected very quickly. The only other allergic history has been to phenobarbital, when the patient was hospitalized for surgery in 1936, and also on rare occasions to shellfish, when laryngeal edema and, less rarely, angioneurotic edema of the face will develop. Please furnish suggestions in regard to diagnosis and treatment.*

M.D., New York.

Answer.—This is a clear instance of hypersensitivity to light. Whether such instances constitute a true allergic phenomenon (antigen-antibody reaction) or a release of a chemical mediator (probably histamine) as a result of direct stimulation from the sun's rays is at present not completely settled. In different individuals the range of the ultraviolet spectrum to which they are sensitive differs. This can be determined by special apparatus with differential light filters. However, from a practical point of view this is not necessary. The observations noted by the inquirer are valid enough. If he wishes, he can confirm them by noting the reaction in a small exposed area of skin, while shielding the rest of the surrounding area, with the ultraviolet lamp as a source of light exposure.

The tolerance to light of those portions of the skin frequently exposed is a significant clue to the therapy in this patient. The subclinical tolerance to a constant light source (preferably an ultraviolet lamp) should first be determined. Then the patient should be subjected to repeated daily doses with gradually increasing exposure. For temporary effect one can use antihistamines or creams containing chemicals (*p*-aminobenzoic acid, for example) which filter out ultraviolet rays.

ULCER ACTIVITY AND TRAUMA

To the Editor:—*A 62-year-old man has had acute, massive, upper gastrointestinal bleeding, requiring multiple transfusions and hospitalization. He attributes his illness to an accident occurring four days prior to hospital admission, when the horse he was riding jumped. He states that at that time he experienced sudden, burning, severe pain in the epigastrium at the upper pole of an abdominal incision; this pain lasted for approximately one hour. His history has included "ulcer trouble" off and on for 35 years. He was operated on for a perforating ulcer 24 years ago; he had a gastroenterostomy for persistent ulcer symptoms 25 years ago; two years ago he had a subtotal gastrectomy for persistent symptoms and hemorrhage. The second day of admission an upper gastrointestinal series was performed, which revealed an altered mucosal pattern suggesting edema at the anastomotic area; however, no ulcer was demonstrated. Barium-meal test done two weeks later revealed a more normal mucosal pattern and an apparently wider opening at the anastomosis. What is an opinion as to the relationship between the ulcer and trauma?*

M.D., California.

Answer.—Obviously this is a man who has a definite tendency to create a peptic ulcer as long as he has any free acid in his stomach. Following his operation two years ago he was well until trauma occurred as a result of his horse's jumping. Following the trauma he had a massive hemorrhage, undoubtedly from the stomach. The question posed is the relationship of the so-called trauma to the immediately succeeding symptoms. The postulates of

Liniger and Molineus regarding trauma and internal disease are as follows: 1. The trauma must be severe. 2. The symptoms must occur within 24 or 48 hours after the trauma. 3. The symptoms must be characteristic of the disease. 4. The disease must run the usual course characteristic of it.

It does not appear that the trauma was sufficient, but it may well have been. It is difficult to say how violent was the reaction of the man to the violent jerk of the horse. The symptoms which appeared immediately were characteristic of hemorrhage from ulcer or ulceration in the stomach and followed the course of such a hemorrhage. It is presumed that this patient had a degree of gastritis, such as is common at the stoma following subtotal resection for ulcer, and that trauma within an hour activated the serpiginous ulceration and created hemorrhage. The fact that the gastrointestinal series performed two days after admission to the hospital revealed merely an altered mucosal pattern does not exclude ulcer. The prognosis should be good but, if hemorrhage recurs, a bilateral vagotomy should be performed.

EYE DAMAGE FROM LYE

To the Editor:—*What are the effects of a mild solution of lye on the eyes—not so much its effect on the anterior segments, such as lids, conjunctiva, and cornea, but more its effect on the accommodation and optic nerve? Two patients who got lye water in their eyes were treated immediately after the accident, with the final result being slight tearing and photophobia, no evidence of scarring in bulbar conjunctivas or corneas, and no pathology in the eyegrounds. They claim a great loss of vision and contracted fields to form and color, for which one is unable to account unless they are malingering. Several malingering tests have been tried, and there is reason to believe that they are trying to deceive us. They are compensational cases.* *M.D., Florida.*

Answer.—Damage to the eyes from the action of mild alkali solutions, if promptly and properly treated, may be expected to be limited to the superficial structures of the eyes and chiefly the cornea and conjunctiva. In severer or neglected cases, an exudative iritis may appear. In gross burns of the eyes, with manifest destructive processes in the superficial tissues, conceivably deeper damage could appear as secondary to the initial action. The absence of obvious damage to the exposed portion of the eye, such as corneal opacities, almost entirely precludes any possibility of injury located exclusively in the interior of the eye. As to penetration, Ryan (*A. M. A. Arch. Indust. Health* **16**:250-253 [Sept.] 1957) states: "Alkalis cause swelling of the skin surface of conjunctiva and cornea, which then becomes soft and jelly-like. The alkali penetrates rapidly and tends to combine with the tissue, so that even long-continued irrigation of the eye does not remove all of it. Some of the alkalis have been detected in the aqueous fluid of the rabbit eye within a few minutes after being placed on the cornea. Alkali burns tend to become progressively worse if the alkali was very strong, remained in contact with the eye for more than a few minutes, or was not irrigated for at least 30 minutes with saline or water."

SPINAL ANESTHESIA

To the Editor:—*A patient was given a spinal anesthetic for an appendectomy, and the level of the anesthesia came to the symphysis pubic area. In order to proceed with the operation it became necessary to supplement the anesthetic with intravenously administered thiopental (Pentothal) sodium, nitrous oxide, or both. Is this dangerous? Is it advisable? Or should the patient be sent back to his room and the operation performed another day? How much greater risk to the patient is there in this kind of anesthesia if the operation is continued on the day it is scheduled?*

M.D., New York.

Answer.—Such an unsatisfactory anesthesia as mentioned, which represents failure of the proper cephalad distribution of the spinal anesthetic agent in the subarachnoid space, may be safely supplemented with either cyclopropane or a combination of thiopental sodium, nitrous oxide, and, if necessary, a muscle relaxant. This is not necessarily dangerous, provided that the patient's state of oxygenation is maintained at a normal level. Rather than attempt to answer the question of whether it is advisable to supplement such an inadequate spinal anesthetic, it would be better to forestall the need for such supplementation. This can be accomplished only if the person performing the spinal anesthetization understands the basic principles involved, particularly how to obtain the proper distribution of the anesthetic agent in the subarachnoid space.

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X-RAY DIAGNOSIS OF FRIEDLANDER'S PNEUMONIA

To the Editor:—*Is it possible to diagnose Friedlander's pneumonia by x-ray?* *M.D., Indiana.*

Answer.—It is possible to make a diagnosis of Friedlander's pneumonia by x-ray examination provided the x-ray findings are fairly typical and some opportunity for serial study is afforded. Obviously,

no such diagnosis is absolute. An extremely dense shadow of consolidation exhibiting bulging outer borders, rapid cavitation, tendency to spread, and very slow resolution are some of the distinguishing features.

TREATMENT OF CHROMOBLASTOMYCOSIS

To the Editor:—*Iontophoresis with copper sulfate is suggested in several textbooks as a possible method of treatment of chromoblastomycosis. Please give particulars of this medication, such as copper sulfate concentration, current density, and voltage needed. Does a "clean" skin need protection from deposit? What is the length and frequency of individual treatment? Can this treatment be advantageously combined with other, such as application of trichloroacetic acid?*

R. A. Bolstad, M.D., Fort-Dauphin, Madagascar.

Answer.—Iontophoresis treatment with copper sulfate was used in one case of chromoblastomycosis (Martin and others: *Am. J. Trop. Med.* **16**:593, 1936) and was described as follows: "The normal areas of the skin were covered with vaselin and the hand and forearm immersed in a bath containing one percent $CuSO_4$. The negative electrode was placed on the upper arm and the positive electrode placed in the bath. A galvanic current of 2.5 milliamperes was passed through the bath for thirty minutes. The treatment was given daily from June 19 to August 2 when the current was increased to 10 milliamperes. This dosage was maintained until the time of discharge on November 23 (approx. four and a half months)." Sulfamerazine may be used to advantage if given over long periods of time.

INTRAVENTRICULAR PRESSURE TRACINGS

To the Editor:—*What is the physiological explanation for the diastolic dip found in right intraventricular pressure tracings in patients with constrictive pericarditis?*

M.D., New York.

Answer.—The diastolic dip found in right intraventricular pressure tracings in patients with constrictive pericarditis is more apparent than real. In the normal individual, the diastolic pressure falls abruptly to zero and with only minor waves gradually rises to 5 to 7 mm. Hg prior to systole. In patients with constrictive pericarditis, the fall in right intraventricular pressure is similar to normal, but the rise is rapid to 10 to 12 mm. Hg, followed by a plateau to about 15+ mm. Hg before systole. The curve described has been termed the "square-root sign." The more rapid rise of intraventricular pressure probably reflects the pressure necessary to distend the somewhat less flexible ventricle and is probably only indirectly related to the size of the constricted ventricle. This same type of pressure change is also found with chronic right ventricular failure, congenital fibroelastosis, and amyloidosis of the myocardium, which also suggests that the square-root-sign curve is produced by the lack of elasticity of the myocardium. In these conditions the curve may be masked by a rapid heart rate but is readily apparent when the rate is slow. This is described by Hetzel and others (*Proc. Staff Meet. Mayo Clin.* **28**:107, 1953).

DERMATITIS OF FIFTEEN YEARS' DURATION

To the Editor:—*A woman, 42 years old, for the past 15 years or more has had a dermatitis on the palmar surface of the hands, with some rash on the feet. This is an itching, pale pink, indurated, dry, and rather scaly eczematoid dermatitis. No fungus has been found. In 1944 the patient received seven or eight x-ray treatments of 70 r each to the hands with only temporary relief. An attempt at desensitization was carried out with an antigen containing all the important local pollens but without benefit. Various ointments have been tried, such as the tar and cortisone preparations as well as ultraviolet-ray exposures and sedatives. The patient wears cotton-lined rubber gloves when washing dishes and at present is obtaining some relief with Silicare lotion. Is there any form of treatment that might be of benefit?*

M.D., California.

Answer.—In the treatment of any dermatitis of the hands and feet, it is essential that an accurate diagnosis be made. If the dermatitis is a simple inflammatory reaction, the etiology must be discovered and eliminated. In view of the involvement of the palmar surface of the hands, there is a good possibility that the eruption is psoriasis. The rebelliousness to all forms of treatment and the negative smear for fungi suggest the possibility of psoriasis.

ABIATROPHY OF ANAL SPHINCTER

To the Editor:—*A woman, aged 67 years, expels gas without having any feeling or sensation that she does it. Please make suggestions for treatment or relief of this embarrassing condition.*

M.D., Iowa.

Answer.—This patient may have an abiatrophy of the anal sphincters, along with the changes that come with her age. This is not an uncommon complaint. It is important that these women avoid the gas-producing foods as much as possible. Of these, there are many. In addition, taking a small amount of charcoal often gives great relief from excessive gas formation and passage of gas. The charcoal should be in powdered form. The patient could place half a teaspoonful of it on the back of her

tongue 10 minutes before each meal, washing it down with a little water without taking a breath. It is important that the details of this administration be followed rather carefully; otherwise, the charcoal will come out of the ears and nose. Charcoal powder is helpful for gaseous indigestion of all kinds, particularly for the excessive formation of flatus.

OCCIPITAL HEADACHE

To the Editor:—*A man, 35 years old, has been subject to recurring daily pains in the back of the neck and occipital headache ever since childhood. They occur mostly in the late afternoon and evening, are relieved by lying down, and are only partly relieved by aspirin. An x-ray examination of the cervical spine reveals a congenital failure of fusion of the spinous process of the second cervical vertebra, appearing in the anteroposterior view in the form of a gap between the two converging laminas. Low-back weakness and backache have often been attributed to congenital anomalies of this type. Is it probable that this anomaly would be the cause of the troublesome symptoms?*

M.D., Ohio.

Answer.—Occipital headache associated with pain in the posterior cervical region is usually a reflex mechanism due to muscle spasm of the posterior cervical muscles, and is frequently observed in all sorts of conditions involving the cervical spine, either postural or mechanical, or due to disease. It is common in hairdressers, stenographers, piano players, and many others who use their arms in the forward position. The statement that relief occurs from lying down is evidence that the patient's posture has a great deal to do with his symptoms. The use of overhead gentle intermittent traction twice a day is most helpful in the experience of this consultant. The anomaly mentioned is rare, and, if it is a cause, the headache would not be relieved much by postural changes.

LOSS OF TASTE AFTER TONSILLECTOMY

To the Editor:—*Loss of taste has occurred in a patient after tonsillectomy. She is a cook, and taste is very essential in her business. Please make suggestions as to further treatment. How long will this condition persist?*

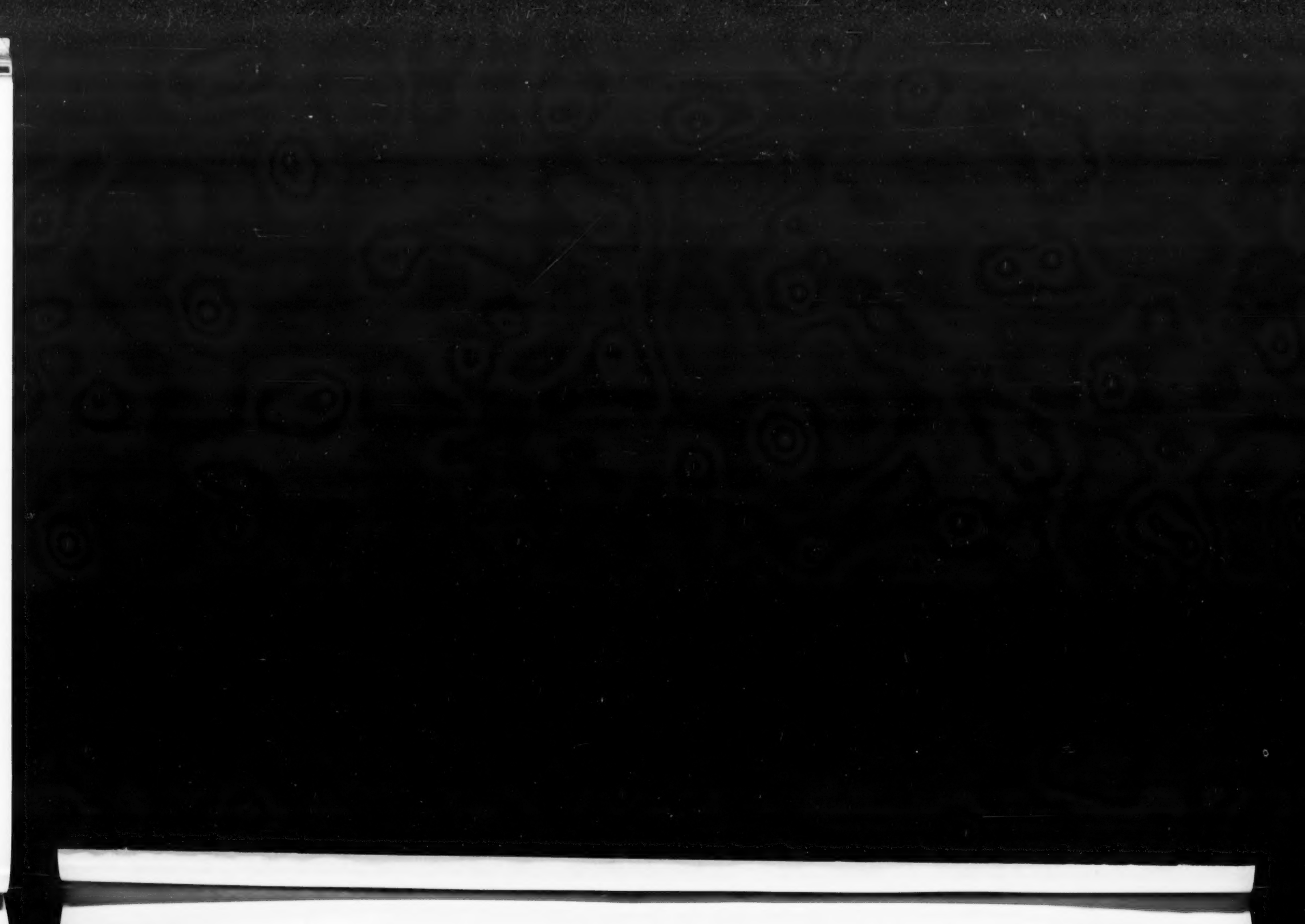
M.D., Washington.

Answer.—Loss of sense of taste as a complication of tonsillectomy is indeed a rare condition. Probably some injury was done to the glossopharyngeal nerve, which supplies taste fibers to the posterior portion of the tongue. However, the anterior two-thirds of the tongue is supplied by the chorda tympani, and certainly could not have been injured during the tonsillectomy. The glossopharyngeal nerve also supplies sensation to the mucous membrane of the pharynx, the fauces, and the palatine tonsil. It is conceivable that some scar tissue may have grown over from the tonsil fossae and areas immediately adjacent to the dissected areas of the tonsil, especially at the lower poles of both tonsils.

A careful inspection of the areas which were operated on is recommended, especially near the posterior portion of the tongue; with the patient under a little local anesthesia, perhaps some of the scar tissue could be removed. Also, the use of vitamin B_{12} injections several times a week and the local application of 95% alcohol to stimulate the taste buds might be considered. In general, the sense of taste should return within 18 months of the time of operation, if there is no central lesion of the brain causing loss of sense of taste and other complications.

"MIXING" CARDIAC GLYCOSIDE DRUGS

To the Editor:—*In "mixing" cardiac glycoside preparations, some physicians accomplish initial digitalization with one type of cardiac glycoside and then switch to another for maintenance. For example, initial digitalization with digitoxin in appropriate doses is given, followed by daily maintenance doses of whole-leaf digitalis. Might not this practice be pharmacologically unsound and result only in a loss of digitalization as the excretion of the digitalizing dose progresses?*

C. A. Imboden Jr., M.D., Johnstown, Pa.

Answer.—There is no reason why digitalis preparations may not be "mixed" as described above. Neither does there seem to be any advantage in such a procedure. When indicated, all the so-called pure glycosides of digitalis and the whole-leaf digitalis itself are almost equally effective in the treatment of heart disease, and they may be changed about at will, provided that one requirement is met. This requirement demands that the attending physician be thoroughly familiar with the dose, the absorption rate, and the excretion rate of the various preparations. It is necessary to maintain an effective concentration in the body of any digitalis preparation in order to obtain the desired result. Also, it is necessary to avoid digitalis intoxication. In order to accomplish this, the physician must be thoroughly familiar with the equivalent dose, the absorption rate, and the excretion rate of each of the preparations, which properties incidentally are different in each preparation. Therefore, unless there is an overriding indication for "mixing," it is probably better to stick to one preparation. However, nothing is lost by "mixing" if it is properly carried out. The main point is that digitalis preparations are given to produce a clinical effect and not to get a certain number of milligrams into the patient.